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TUBULAR INSUFFICIENCY AND RENAL DWARFISM*

BY

G. FANCONI

From the Department of Paediatrics of the University of Zürich, and the Kinderspital, Zürich

(RECEIVED FOR PUBLICATION SEPTEMBER 2, 1953)

Taken as a whole, growth disorders may be attributed to various causes: (1) Lack of building material, especially proteins; (2) disturbance of neuro-hormonal regulation; (3) disorders of metabolism, e.g., in absorption in the intestine, transportation, assimilation or excretion; (4) non-response of the end-organs, i.e., bone and protoplasm in general. In this complex system of vital functions the kidney plays a prominent part because it is not only the organ of elimination for many metabolites, but, also, in its distal tubules, it is a most important seat (end-organ) of many chemical adjustments. If these adjustments fail the state of growth suffers in consequence.

The regulation of the metabolism of water, sodium chloride, calcium and phosphate, dextrose and amino-acids, depends on the interplay of certain mechanisms (Fig. 1).

Mechanism of Growth and its Disorders

The diencephalon acts upon the end-organs directly or through the endocrine glands. The hormones of the endocrine glands get into the extracellular fluid and influence the intestine, the storage organs and the kidneys. Chemoreceptors control the level of the chemical substances in the extracellular fluid and influence the diencephalon and the endocrine glands.

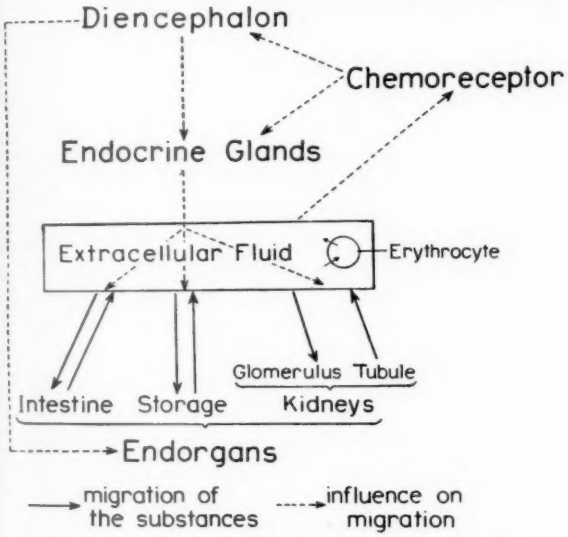

FIG. 1.

The individual members of this hierarchy of mechanisms are mutually dependent. A disturbance in the function of any one member is immediately counteracted by the others. It is often difficult, therefore, in any given case to locate the exact site of the disturbance.

The reabsorption of a large number of substances takes place in the tubules of the kidney in relation to the needs of the body as a whole. This adjusted reabsorption is described as facultative. There are good grounds for the belief that the reabsorption of each of the substances occurs at a different level in the tubule and is dependent on different mechanisms. Dextrose, amino-acids and part of the phosphate are reabsorbed in the proximal tubule. The reabsorption of the base equivalents (the economy of base and the production and excretion of ammonia) or of acid equivalents to maintain the acid base balance takes place in the distal tubule. The reabsorption of the main extracellular electrolytes, sodium and chlorine, as well as water, occurs throughout the whole length of the tubule, but mainly in Henle's loop.

This complex reabsorption process, obligatory as well as facultative, may be upset in one of two ways: the reabsorption may be excessive or insufficient. In the case of dextrose and amino-acids, normally completely reabsorbed, there is but one possibility, insufficient reabsorption causing renal glucosuria and amino-aciduria. For the other substances, however, instances of pathologically decreased and increased reabsorption are both known: (1) for water, on the one hand diabetes insipidus, on the other oliguria as in lipoid nephrosis; (2) for sodium chloride, on the one hand diabetes salinus renalis (salt-losing nephritis), on the other hand renal hyperelectrolytaemia as in Cushing's syndrome. (3) In phosphate diabetes (hypophosphataemic

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vitamin D-resistant rickets) too little phosphate is reabsorbed, whereas in true and pseudo-hypoparathyroidism too much is reabsorbed. (4) Lightwood-Albright's tubular renal acidosis ensues if the reabsorption of inorganic bases is impaired. This may be due either to an insufficiency of H ions released from bicarbonate by carbonic anhydrase in the urine, or may be related to an insufficient formation of ammonia by the kidney.

In the literature various disorders related to an insufficiency of reabsorption at the level of the proximal tubule have been labelled Debré-de Toni-Fanconi's syndrome. Those related to an insufficiency of reabsorption at the level of the distal tubule have been called Lightwood-Albright's syndrome. These terms have caused much confusion and it would be better to use the more exact terminology 'proximal tubular or distal tubular insufficiency'. Darmady (personal communication) demonstrated in cases with insufficiency of the proximal tubules the cellular atrophy (narrow neck) in the proximal tubules by dissection of individual nephrons as well as in paraffin sections.

In practice, the diagnosis of tubular insufficiency is much more complicated, for the following reasons. First of all, the initial disorder does not always originate in the tubule itself, but may be located at another level of the hierarchy of regulatory mechanisms without any noticeable change in the symptoms, as for example in diabetes insipidus or hypoparathyroidism. For the regulation of water and sodium chloride the chief end-organ is the distal tubule. The osmoreceptor is probably located in the nucleus supra-opticus of the diencephalon. We have two groups or two hormones which control excretion in the tubules, a hormone from the posterior lobe of the hypophysis, the adiuretin or pitressin, and the salt-hormone produced by the adrenals, and this depends on the A.C.T.H. excreted from the anterior lobe.

The same symptoms can be produced by disturbances at various places in the complicated system of regulation. For example, isothenuria, that is, the impossibility to concentrate the urine, may be due to a primary insufficiency of the renal tubule or to a disturbance in the hypothalamic-pituitary system.

The second reason why diagnosis is complicated is that the disorders which affect the enzymes regulating tubular reabsorption (usually phosphatase and phosphorylase) may be generalized to a varying degree, with the result that the prominent symptoms are those of a generalized metabolic disorder such as cystinosis of the organs or glycogenosis of the liver.

Third, the disorder of reabsorption may extend simultaneously to several levels of the tubule and affect them in varying degrees (Table 1).

In the completely developed Debré-de Toni-Fanconi syndrome there is not only an insufficiency of the proximal tubule, but also a defective excretion of base equivalents, whereas excretion of ammonia is normal or slightly increased. There are, however, diseases like phosphate diabetes or renal glycosuria in which only one function of the proximal tubule is concerned. In the tubular renal acidosis of Lightwood-Albright not only the function of the distal tubule, but probably also the elimination of phosphate is altered. Indeed Latner and Burnard (1950) were able to show that an increase of the serum phosphorus improved the excretion of ammonia and the elimination of acid equivalents in the urine.

Thus a whole set of clinical pictures is derived from various such combinations. If we wanted to

TABLE 1
SOME EXAMPLES OF TUBULAR DISORDERS

Diseases	Whole Tubule		Proximal Tubule			Distal Tubule	
	Water	Na & Cl	Phosphates	Amino-acids	Dextrose	Base Equivalents	NH^3 Production
Diabetes insipidus normochloraemicus	−						
Diabetes insipidus hyperchloraemicus	−	+					
Lipoid nephrosis	+	+					
Diabetes insipidus occultus		+					
Cerebral hyperelectrolytaemia		+					
Diabetes salinus renalis		−					
Hypercorticism		+					
Phosphate diabetes (Vitamin D-resistant Rickets)			−				
Renal glycosuria					−		
Debré-de Toni-Fanconi syndrome			−	−	−	−	?
True and pseudo-hypoparathyroidism			+				
Hyperparathyroidism			−				
Tubular renal acidosis (Lightwood-Albright)			?			−	−

Tubular reabsorption or NH^3 production increased = +
Tubular reabsorption or NH^3 production decreased = −

describe each combination of disturbed functions in the tubular or in the hierarchy of regulatory mechanisms as such, we would never come to an end. Diagnosis and therapy are better served if, instead of thinking in terms of rigid, strictly defined nosological entities, we reason functionally, seeking to locate and evaluate the seriousness of the disorder as completely as possible. In what follows we have tried to analyse some clinical entities by this functional method.

Forms of Diabetes Insipidus

TABLE 2

Factors (functions) regulating extracellular fluid

(*a*) Tubular reabsorption of water.
(*b*) Tubular reabsorption of Na^+ and Cl^-.
(*c*) Adjustment of the osmolarity by the osmoreceptors.

Clinical syndromes	*Disturbed Function*
Diabetes insipidus hyperchloraemicus	*a, b, c*
Diabetes insipidus normochloraemicus	*a*
Responsive to pitressin	
Non-responsive to pitressin	
Diabetes insipidus hyperchloraemicus occultus	*b, c*
Neurogenic hyperelectrolytaemia	*c*

It has always been evident that several forms of diabetes insipidus exist. In 1946 we drew attention to the fact that the various forms of diabetes insipidus could be differentiated according to the special functions which were upset in the excretion of water and NaCl (Fanconi, 1946). It is indeed possible to distinguish three such special functions which are not necessarily associated; (1) the regulation of tubular reabsorption of water, (2) the regulation of reabsorption of NaCl and (3) the adjustment of Cl and Na levels in the extracellular fluid, probably brought about by the osmoreceptors in the nucleus supra-opticus of the hypothalamus.

The first and second of these special functions are partly antagonistic, as an increase in the osmotic pressure of the extracellular fluid can equally well be counteracted by water retention, as by increased NaCl excretion. According to which of these three special functions is disturbed, the distinction can be made between the different forms of diabetes insipidus.

Hyperchloraemic Diabetes Insipidus.—The hyperchloraemic form of diabetes insipidus is mainly found when there is an important lesion of the hypothalamic-pituitary system. In this case all three special functions are upset and the diagnosis is easily made.

Normochloraemic Diabetes Insipidus.—In the normochloraemic form water excretion alone is upset, because the facultative reabsorption is insufficient in relation to the needs of the body as a whole. It is astonishing how the organism manages to maintain constant the osmotic pressure of the extracellular fluid despite considerable loss of water. One cannot help thinking that a protective mechanism must come into play. During dehydration such a mechanism could bring about the storage, somewhere in the body, of NaCl in a dry (osmotically inactive) form. Mild cases of this form are difficult to distinguish from primary polydipsia as the limits are probably not clear cut. In any case we have observed several cases which, as they had a reasonable concentrating ability, appeared to be primary polydipsia but had later to be reclassified as diabetes insipidus. Veil (1920) was struck long ago by the fact that some of these cases did not respond to pituitrin, and in 1926 we described such a case in detail (Haymann and Fanconi, 1926). Such cases belong to the category of pitressin-resistant diabetes insipidus, named 'water babies' by American authors, a condition in which the disturbance probably occurs in the end-organ itself, namely in the kidney tubule.

Diabetes Insipidus Occultus.—There are also forms in which the first special function, that of water reabsorption, does not appear upset, as may be the case at the beginning of the disease with infants or at the end of the disease when the anterior lobe of the pituitary has been severely damaged by a tumour. We already suggested in 1937 that these forms should be called diabetes insipidus occultus (Fanconi, 1938).

For example, a 12-year-old girl was admitted to hospital with typical diabetes insipidus hyperchloraemicus, excreting daily 5 litres of urine of a specific gravity of 1005. The serum chloride was always high. But with the aggravation of the disease the diabetes insipidus gradually improved. The volume of the urine decreased to 500 ml., the specific gravity increased to 1020 and more, but the serum chloride increased more and more. Following a single dose of 7 gr. of sodium chloride by mouth, a test which was easily tolerated five months before, the child died three days later, with the chemical symptoms of salt-intoxication. We found a tumour of the brain, a glioblastoma multiforme of the hypothalamic region growing slowly and having infiltrated the posterior lobe of the hypophysis. The anterior lobe of the hypophysis did not seem to be affected, but it is very difficult to be sure that it was functionally unaltered.

We also had the opportunity of seeing two brothers, infants who later on developed typical diabetes insipidus hyperchloraemicus. In their infancy they had permanent fever without any detectable cause. The serum chloride level was very high. In both cases the fever disappeared when water was given or when the intake of salt was decreased. Although the serum chloride has remained high, the boys are still alive.

Neurogenic Hyperelectrolytaemia.—There is also a fourth form in which polyuria is always absent. Therefore it has nothing to do with diabetes insipidus. In 1946 we called this a special form of occult diabetes insipidus, but now we had better say with Cooper, 'neurogenic hyperelectrolytaemia', (Cooper and Crevier, 1952).

Children with this disease are continually at the limit of dehydration, with fever in the morning. They gain little or no weight, and present, therefore, a picture of severe, unyielding malnutrition. In our experience there are two forms, the one which is incurable and which is probably due to the lack or the destruction of the osmoreceptors, and the other, less severe, and probably due to the retarded development of the osmoreceptors. Children having the latter form are generally treated with all kinds of antibiotics that do nothing to bring down the fever. Only a salt-poor diet, plentiful in liquid, can improve the symptoms. After some years the mildly affected tolerate an ordinary diet. A mild hydrocephalus or a dilatation of the third ventricle as shown by pneumo-encephalography are signs of a primary cerebral disorder.

In one case the child presented certain kidney symptoms, a mild proteinuria and bacteriuria etc. Therefore we were not sure whether the condition was neurogenic hyperelectrolytaemia or renal acidosis (Lightwood-Albright). Indeed, in the beginning the child was not able to concentrate urine. One year later, this was possible. The response to ammonium chloride was completely normal and we could not demonstrate an insufficiency of the distal tubule, but the test was made when the child had already improved.

Debré-de Toni-Fanconi Syndrome

In a recent very important monograph (Bickel, Baar, Astley, Douglas, Finch, Harris, Harvey, Hickmans, Philpott, Smallwood, Smellie and Teale, 1952) Bickel considers cystinosis to be a necessary symptom and he proposes to call the cystine-storage disease with amino-aciduria and dwarfism Lignac-Fanconi disease, even though, at one time, Bickel himself published with me (Fanconi and Bickel, 1949) a case in which proximal tubular insufficiency was accompanied by liver glycogenosis but all signs of cystinosis were lacking. Bickel would now strictly differentiate this nosological entity from the Lignac-Fanconi disease. Proximal tubular insufficiency has also been described in adults (Dent, 1946, 1947, 1952; Lambert, de Heinzelin de Braucourt and Bruneel, 1953). In these cases there is no accumulation of cystine and an intake rich in phosphate and alkali has a definitely beneficial effect. Weber from the Hungerlands Clinic (Weber, 1953) reports a case of cystinosis without any amino-aciduria or hypo-phosphataemia, or hyperphosphataemia, but which shows an insufficiency in the distal tubule. Moreover Bickel holds the opinion that amino-aciduria in the Lignac-Fanconi syndrome is a result of an overflow of amino-acids accumulated in the blood. In contradiction, as he has obtained very high amino-acid clearances, Dent has been able to show that in most cases it is a question of renal insufficiency. The task for future research will be to study the clearance of amino-acids, not as a whole, but individually as it is already known that each one has its more or less independent metabolism. The variations of the Fanconi syndrome will be better understood when we consider the various functional defects of the proximal and distal tubule as well as cystinosis as frequent but not indispensable symptoms. This view is stressed by the fact that the more the science of heredity advances, the more it shows that many special functions may be separately upset. It would be a step forward in scientific thinking if one reasoned less in terms of rigidly defined nosological entities and more in terms of special functions.

Renal Disease with Dwarfism

TABLE 3

A. Chronic glomerular and tubular insufficiency (non-protein nitrogen increased).

(1) Congenital renal malformations with secondary interstitial nephritis:
  (*a*) Without osteopathy (serum phosphorus normal)
  (*b*) With osteopathy (serum phosphorus increased)
(2) Primary and secondary chronic nephritis without malformations
(3) Chronic renal (?) hypercalcaemia with osteosclerosis
(4) Terminal condition of B.

B. Chronic tubular insufficiency (non-protein nitrogen and phosphorus not increased).

(1) Diabetes salinus ('salt-losing nephritis') usually combined with *A*(1) or *A*(2)
(2) 'Phosphatic diabetes' (Vitamin D-resistant rickets)
(3) 'Amino-diabetes' (Debré-de Toni-Fanconi) with and without cystinosis
(4) Renal hyperchloraemic acidosis with nephrocalcinosis (Lightwood, 1935, 1946; Albright, Consolazio, Coombs, Sulkowitch and Talbott, 1940; Albright, Burnett, Parson, Reifenstein and Roos, 1946)
(5) Renal hypochloraemic acidosis with late rickets (Boyd and Stearns, 1941, 1942)
(6) Oculo-cerebro-renal syndrome (Lowe, Terrey and MacLachlan, 1952)
(7) Osteopathia acidotica pseudorachitica (Fanconi, von Albertini and Zellweger, 1948)
(8) Nephronophthisis with primary tubular and secondary total renal insufficiency (Fanconi and co-workers)

'Renal dwarfism' is the title of my lecture. Not every renal disease causes dwarfism. For example, renal glycosuria and the chronic benign pyelitic or post-pyelitic hypertension described in our clinic does not do so (Fanconi, Rüegg and Dieterle, 1951). One of our patients, who is now 32 years old, has had a hypertension since the age of 10; at the age of 11 we found a very severe alteration of the fundus oculi. Fourteen years later the fundus

was normal and the young man is now very well, although the hypertension persists. In another case of benign post-pyelitic hypertension existing from the first year of life we found at the age of 19 years a unilateral dilatation of the calices of the pelvis as a scar of the infection during infancy. The serum chemistry of this girl was the opposite of that found in tubular renal acidosis as the alkali reserve was very high (77 vol. %) and the chlorine was normal or decreased (326 mg. %).

Furthermore the familial disease 'nephronophthisis', also described in our clinic, does not influence growth, at least not in the first period when the disturbance is only located in the distal tubule (Fanconi, Hanhart, von Albertini, Ühlinger, Dolivo and Prader, 1951).

I should like to draw your attention to congenital malformations with hyperphosphatemic osteopathia (Table 3, 1*b*), because in these cases we have frequently a combination with a renal hyperchloraemic acidosis and diabetes salinus renalis.

One of our patients, a boy of 16 years, had a very serious form of this disease. We observed him in our hospital at the age of 13 in 1937. As he had nephritis, we gave him a salt-free diet. After two weeks he presented all the symptoms of uraemia with symptoms of latent tetany. The level of serum chloride being very low, we fortunately decided to give him salt both orally and intravenously. The symptoms of uraemia disappeared very quickly. We made the diagnosis of diabetes renalis salinus and some months later we cautiously repeated the experiment with a salt-free diet. The child continued excreting chloride in the urine, he had lost the power of facultative reabsorption and the serum chlorine decreased, the general condition got worse and we were obliged after three weeks again to prescribe salt in the diet. Some days later he improved once more. The concentration of chlorine in the urine had decreased only a little during the salt-free period. To protect the body from too great a loss of NaCl the volume of urine decreased also. But this is a two-edged knife. By the reduction of the volume of urine it is not possible to excrete the scoriae of the metabolism and the azotaemia as well as the phosphaturia increases. With this experience we proved that we were really concerned with a salt-losing nephritis. Three years later the child died. The contracted kidney showed enlarged tubules with a very thin epithelium. We can well understand that the facultative reabsorption of NaCl corresponding to the needs of the whole body by such altered tubules is not more possible.

In this and other cases we find the signs of fibro-osteoclasia in the bones and in radiographs the signs of secondary hyperparathyroidism. The phalanges show the typical subperiosteal bone reabsorption, the skull a granular atrophy. But in the metaphysis of the long bones we find also signs of renal rickets with proliferation of the osteoid tissue. This is probably not the consequence of the secondary hyperparathyroidism but of the acidosis.

This year we had the opportunity of making further observations on a boy 17 years old with the same disease. He excreted about 3,000 ml. of urine daily, day and night in the same quantity, and in the same low concentration. Other tests also demonstrated a complete isosthenuria. The analysis of the serum showed a certain degree of insufficiency of the glomeruli, and also of the distal tubule as in the Lightwood-Albright syndrome; that is, a marked chlor-acidosis. Unfortunately we could only make brief observations. The alkali therapy improved the hyperphosphataemia. Although the calcium level was very low, the kidney continued to excrete calcium. After treatment this excretion of calcium and also of the other kations Na and K decreased. The most striking point was the lowering of the phosphate level after the alkali therapy.

But alkali therapy is only possible if the glomerular function is sufficient. In another similar case we produced a very dangerous hyperelectrolytaemia by this therapy. The child died and we found in the bones a significant fibro-osteoclasia, a sign of secondary hyperparathyroidism. This case was sent to the hospital with the diagnosis of Cushing's syndrome, because the child was very fat. We spoke of a renal pseudo-Cushing syndrome. It is possible that chronic kidney disease causes a chronic stress. This could induce the adrenals to produce a larger amount of catabolic S hormones and so inhibit the growth and facilitate the deposit of fat.

To conclude we must try in these cases of nephropathy to avoid a loss of NaCl because of diabetes salinus renalis, and a loss of inorganic base because of the insufficiency of the distal tubule. But on the other hand we must also avoid hyperelectrolytaemia by giving too much salt and alkali. The fibro-osteoclasia and the osteomalacia can be cured by large doses of vitamin D, and in some cases dehydrotachysterol may be tried.

The cases described by Schlesinger and his colleagues in London and in our clinic in Zurich (Fanconi, Girardet, Schlesinger, Butler and Black, 1952) prove that nephropathy with glomerular insufficiency can also produce chronic hypercalcaemia with osteosclerosis combined with a retardation of growth. In these cases the product of calcium and phosphorus in the serum is so high that an osteo-sclerosis must result.

Another form of renal retardation of growth is the phosphate diabetes with vitamin D-resistant rickets. We believe that this hereditary disease of the dominant type is the consequence of an insufficient reabsorption of phosphate in the tubules. This disease, which is not at all rare, must be treated with enormous doses of vitamin D.

Finally I must mention a case of renal osteoporosis without osteomalacia which represents perhaps a new type of nephropathy and for which we proposed the name of 'osteopathia acidotica pseudorachitica'. Treatment with vitamin D rapidly improved the osteopathy. The serum chemistry corresponds to that found in the Lightwood-Albright renal acidosis with the difference that the phosphatase is very high (Fanconi *et al.*, 1948).

With this exceptional case I wish to end my long lecture, in which I find that I have raised more questions than I have answers to give.

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A REPORT OF SEVEN CASES OF CHONDRO-OSTEO-DYSTROPHY (MORQUIO'S DISEASE)

BY

W. F. TOWNSEND-COLES

From the Civil Hospital, Khartoum, Sudan

(RECEIVED FOR PUBLICATION OCTOBER 7, 1953)

Since its first description by Morquio (1929) this disease has been observed in most European races and in coloured people but has not been reported, so far as I am aware, from the Sudan. To 71 cases reported in the world literature (Whiteside and Cholmeley, 1952) are added seven in three northern Sudanese families. It would not be surprising if abnormalities transmitted as Mendelian recessives were found to be relatively common in a community where consanguineous marriage is the rule rather than the exception.

General Description of the Affected Children

The families of these children were in good circumstances and they had been well fed and well cared for. All six parents appeared healthy and had negative blood Kahn reactions. The affected children were said to have been healthy at birth and to have remained so until the seventh or eighth month when deformity became manifest by gradually increasing kyphosis except in Case 1 in which chest signs were first noticed. The children were being or had been breast fed for the first two years and they had all received cod liver oil in the belief that they were rickety. They had had frequent 'colds', 'bronchitis', 'cough with fever' or 'pneumonia', of which the patient in Case 2 had died.

All the patients showed dwarfing and deformity which were more marked the older the child. The normal development of the head made it appear large by comparison with the stunted trunk and limbs, and the excessive shortening of the trunk gave the arms a false appearance of length. The deformities included shortness of the neck, antero-posterior enlargement of the chest, eversion of the costal margin, pointing of the sternum and dorsi-lumbar kyphosis. The limb bones were short but enlarged at the ends giving the joints a swollen appearance. The large olecranon processes prevented full extension of the elbows and there was ulnar deviation of the hands at the wrist joints. Genu valgum and partial flexion of the knee joints were present and the feet were short, wide, flat, and everted at the ankle. Marked laxity of the muscles and ligaments allowed the joints undue mobility. The milk teeth were well formed but in the two oldest living children the permanent teeth were poor in quality. Dyspnoea at rest was also noted in these two older and more deformed patients. In all the intelligence was normal.

Radiologically the skull and pituitary fossa were normal. The vertebrae were flat, irregular in shape and texture, poorly calcified and drawn out in front to a point which was most marked in the dorsi-lumbar region. The intervertebral spaces were deep (Fig. 3). The antero-posterior diameter of the pelvic brim exceeded the transverse (ape pelvis) and the acetabular roofs were irregular (Fig. 13). The ends of the ribs were abnormally wide. The long bones were short, thick, and poorly calcified. The cortices were thin and the cancellous tissue showed coarse and irregular reticulation. The metaphyses were irregular, expanded, and in some cases cup shaped. Large irregular epiphyses contained fragmented or multiple ossific centres. The joint spaces were wide. Coxa valga and thickness of the femoral necks were associated with flattened femoral heads (Fig. 13). The proximal ends of the metacarpals and metatarsals were characteristically conical (Fig. 8 and 17).

The First Family

Of the reputedly unaffected children of this family it has been possible to examine only the youngest

who was healthy. In a 10-year-old photograph of the whole family the rest appeared normal.

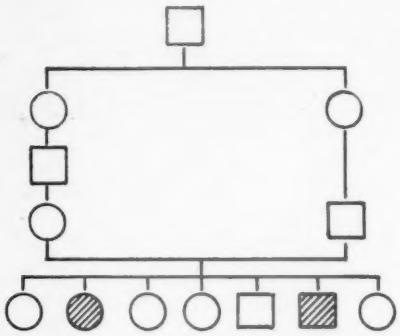

FIG. 1.—Pedigree of Family 1.

Case 1.—A girl of the first family (Fig. 2), aged 21 years (height 34½ in., weight 41 lb., head circumference 21¼ in.), was said to have had 'asthma' at 3 months and to have shown deformity first in the chest at 7 months of age. She crawled at 18 months and walked between the second and fourth years. Thereafter she gradually stopped walking with increasing deformity. Catamenia started at 18 years and had been regular since.

At the age of 21 this girl was a severely crippled and deformed dwarf who could neither stand nor walk

FIG. 2.

FIG. 3.

FIG. 2.—Case 1 at 21 years.

FIG. 3.—Spine of Case 1 at 21 years showing anterior projections of vertebral bodies.

and was unable to raise herself from lying to sitting. She was breathless at rest and the laxity of the muscles and ligaments was very marked. The liver could be felt three fingerbreadths below the costal margin in a protuberant abdomen. The breasts were well developed, and pubi: but no axillary hair was present. She had all but thre: wisdom teeth of her permanent dentition but they wer: poorly formed and pyorrhoea was severe. Although the radiograph (Fig. 3) shows the characteristic malforma tion of the vertebral bodies, there was no kyphosis bu merely absence of the normal lumbar lordosis.

She was said to have been very miserable since the death of her brother because she now felt she was the only deformed dwarf in the world.

FIG. 5.—Forearm of Case 2 at 14 years showing characteristic deformities at ends of radius and ulna but slenderness of their shafts (Dr. M. Hassan's case).

FIG. 4.—Case 2 at 4 years (Dr. M. Hassan's case).

Case 2.—This was a boy aged 14 years at the time of death in February, 1953, from pneumonia. He was not seen but was described as a deformed dwarf. A photograph taken at the age of 4 (Fig. 4) reveals well-marked deformity. Radiographs taken shortly before death show characteristic changes in the vertebrae.

X-ray pictures of the long limb bones of Cases 1 and 2 presented characteristic metaphyseal and epiphyseal abnormalities but the shafts, unlike those of the patients from the other two families, were slender rather than thick. Cases 1 and 2 were older and more severely crippled than the others, and it seems probable that the thinness of the long bone shafts (Fig. 5) was due to atrophy from disuse.

The Second Family

The first and second children of this family had died at 45 days and a few minutes after birth respectively and there was no other information

about them. The third and fifth were examined and found healthy.

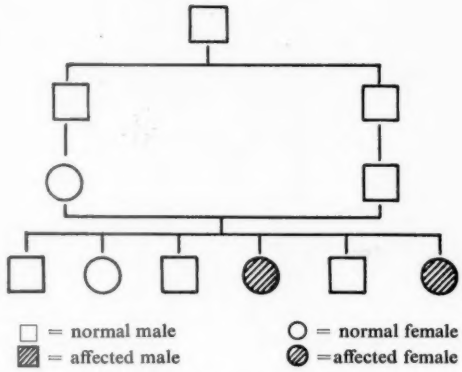

FIG. 6.—Pedigree of Family 2.

Case 3.—A girl (Fig. 7) aged 6 years (height 32 in., weight 27 lb., head circumference 20 in.) had a full milk dentition and all four sixth-year molars. The clinical and radiological signs of the disease were advanced (Fig. 8) and Harrison's sulcus was well marked on both sides of the chest. The liver extended two fingerbreadths below the costal margin.

FIG. 7.—Case 3 at 6 years showing characteristic deformities and well-marked Harrison's sulcus.

Case 4.—A girl (Fig. 9) aged 14 months (height 27 in., weight 18½ lb., head circumference 17½ in.) was still on the breast and had a fontanelle which was almost closed. There was right congenital talipes equino-varus. A marked dorsi-lumbar kypho-scoliosis had its convexity to the left and in the radiograph (Fig. 10) the lumbar vertebrae were seen to be asymmetrical and irregular. Because of the youth of this child the radiological changes in the bones, although definite, were not gross.

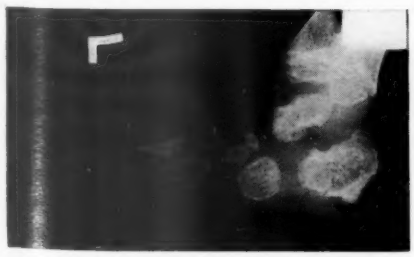

FIG. 8.—Foot of Case 3 at 6 years showing coarsely reticular cancellous tissue in tarsus and conical proximal metatarsal extremities.

FIG. 10.—Spine of Case 4 at 14 months.

FIG. 9.—Case 4 at 14 months showing early dorsi-lumbar kyphosis and enlarged wrists.

The Third Family

The father of this family was a half brother to the father of the second family, the two having the same father but different mothers. Similarly the mother was half sister to the mother of family 2, sharing with her the same father. The eldest child of this family was a healthy boy of 10 years and the youngest was a baby girl of 3 months who manifested neither clinical nor radiological evidence of the disease. The father of family 3 had another family of seven healthy children, four boys and three girls, ranging

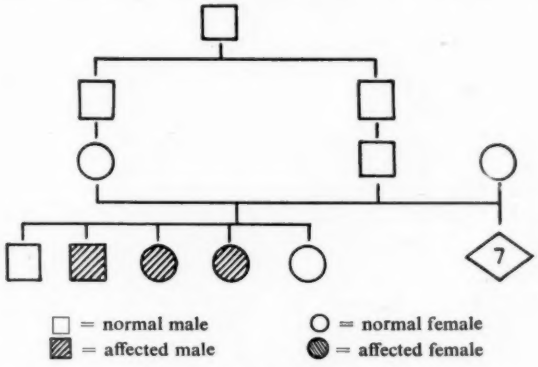

FIG. 11.—Pedigree of Family 3.

in age from 2 months to 13 years, by a second wife to whom he was not a blood relation.

FIG. 12.—Case 5 at 8 years showing general deformity.

Case 5.—A boy (Fig. 12), aged 8¼ years (height 52½ in., weight 30½ lb., head circumference 20¼ in.), was dyspnoeic at rest but could stand and walk unaided. All the left lower teeth were missing except the two incisors. Of the permanent teeth he had erupted three first molars and the two lower central incisors. The permanent incisors were poor in quality being small, yellow, and having serrated free margins. Both testicles were in the scrotum. This boy was markedly deformed and dwarfed by the disease and the radiographs showed advanced bone changes (Fig. 13).

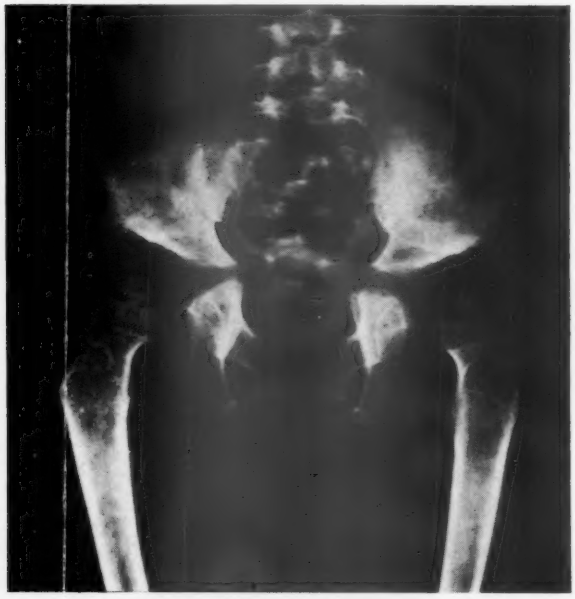

FIG. 13.—Pelvis of Case 5 at 8 years showing 'ape pelvis' and coxa valga.

Case 6.—A girl (Fig. 14), aged 4 years (height 28¼ in. weight 23½ lb., head circumference 19¼ in.), had conjunctivitis with a convergent squint. Nasal discharge had excoriated the skin around the nares. An enlarged lymphatic gland was felt at each jaw angle. The liver extended two fingerbreadths below the costal margin.

FIG. 15.—Humerus of Case 6 at 4 years.

FIG. 14.—Case 6 at 4 years.

In the skeletal deformities this girl strongly resembled her brother but the changes were of lesser degree (Fig. 15).

Case 7.—A girl (Fig. 16), aged 2 years (height 28 in., weight 19½ lb., head circumference 19¼ in.), had conjunctivitis and a liver which extended three fingerbreadths below the costal margin. The only marked deformity was the kyphosis in the dorsi-lumbar region. Pointing of the sternum, eversion of the lower ribs, enlargement of the wrists, ulnar deviation of the hand, genu valgum, knee flexion and pes planus were present but not gross. The radiograph of the hand and wrist (Fig. 17) was highly characteristic as it was in all the other cases.

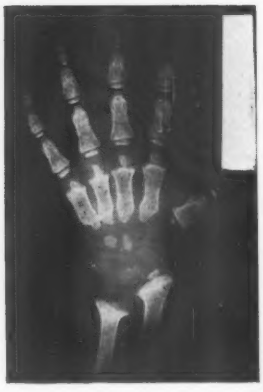

FIG. 17.—Wrist and hand of Case 7 at 2 years showing deformities of radius and ulna, and conical proximal ends of metacarpals.

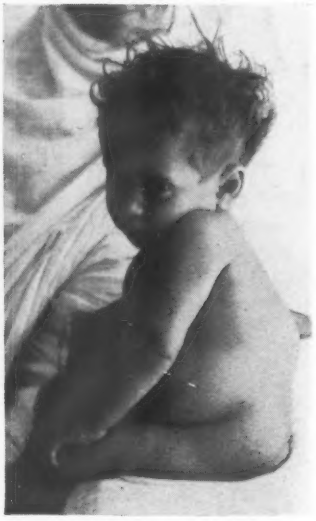

FIG. 16.—Case 7 at 2 years showing dorsi-lumbar kyphosis and enlarged wrists.

Discussion

Morquio's disease is usually regarded as being transmitted as a Mendelian recessive and the patients described here, being of both sexes and the offspring of nearly related parents, conform to this view. Occurrence of the disease in previous generations was denied but there was no opportunity to confirm this statement, which is the usual Sudanese reply to an enquiry into the family history. Of special interest is the attempt of the father of the third family to control his experiment in human genetics by simultaneously marrying a second wife to whom he was not a blood relation and producing by her seven healthy children of both sexes. Jacobsen (1939) described a family in which the transmission was as a sex-linked recessive. All 20 cases were males and had inherited the condition through their mothers.

These cases fit into Brailsford's (1948) generalized and progressive type of the disease. Most of the radiological characteristics described by him have been found in the radiographs of these children. The earliest and most easily recognized features are found in the radiographs of the spine and the hand, the anterior projection of the vertebral bodies and the conical proximal extremities of the metacarpals being highly characteristic.

Palpability of the liver was found in a number of these patients but no spleens were felt. It seemed that the liver was displaced downwards by the chest deformity and was not pathologically enlarged.

The permanent teeth when present were poorly formed and the oldest patient had severe pyorrhoea. This was in contrast to the milk teeth which were uniformly good.

Summary

Seven cases of chondro-osteodystrophy occurring in three sets of siblings in northern Sudanese families are described. In each set the parents were close blood relatives. One father had simultaneously produced a large family of healthy children by a second wife to whom he was not a blood relation.

I wish to thank Dr. J. F. E. Bloss for the photography, and Mr. R. B. Webb for the radiography of these patients. I am grateful to Dr. Mohamed el Hassan Abu Bakr for much help and advice. My thanks are due also to Dr. Mahmoud Mohamed Hassan for information about, and radiographs of the deceased child, and to the Director of Medical Services, Sudan Government, for permission to publish the case records.

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NON-INFLAMMATORY LARYNGEAL STRIDOR IN INFANTS

BY

JAMES CROOKS

From The Hospital for Sick Children, Great Ormond Street, London

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'Congenital laryngeal stridor' is merely a clinical description, and although perhaps 90% of stridors in young babies are due to an exaggerated pattern of infantile larynx, which rectifies itself with increasing age, it is not safe to assume that this is the cause of the stridor. There are other conditions causing laryngeal stridor in young babies, sometimes from birth, which are graver than the exaggerated infantile larynx, and often prove fatal, and which may be amenable to surgical treatment.

Laryngeal stridor in infants is predominantly inspiratory because the infant's larynx narrows on inspiration and blows open on expiration, as is shown in Fig. 1.

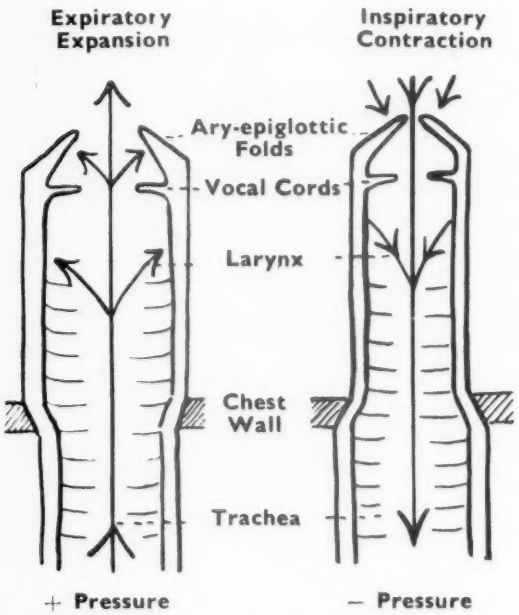

FIG. 1.—Infant larynx.

Inspiratory laryngeal collapse of infants is the best name for 'congenital laryngeal stridor' due to an exaggerated infantile type of larynx as suggested by Schwartz in 1944. The larynx has a folded epiglottis so that its posterior edges with the anterior attachment of the ary-epiglottic folds are close together. These folds are lax. The whole epiglottis is apt to lean back over the entrance to the larynx. On inspiration the soft larynx collapses because of the negative pressure within it, and the epiglottis falls farther back and the now even more lax ary-epiglottic folds fall towards each other and vibrate, causing the crowing noise. On expiration the stream of air of increased pressure blows open the larynx and blows apart the ary-epiglottic folds so that expiration is easy and noiseless. These babies often have micrognathia, and the effect of the small mandibular arch is to force the tongue backwards, causing laxness of the pharyngo-epiglottic folds, and allowing the epiglottis to remain folded and fall back over the larynx. When the tongue is hooked forward by the finger the crowing inspiration often ceases. As the child grows the epiglottis becomes less folded, and the ary-epiglottic folds lie farther apart; the laryngeal cartilages become firmer so that they do not tend to collapse from the negative pressure of inspiration, and the mandible improves in shape.

Inspiratory arytenoid prolapse is suggested as the name for another type of congenital laryngeal stridor which the baby outgrows. The inspiratory noise is much coarser and often louder than the crowing of typical inspiratory laryngeal collapse, and in some case notes the noise is described as a rattle. In these babies it is found that the ary-epiglottic folds are lax, but the epiglottis is not folded so that they are not abnormally close together. But the arytenoids are prominent and have usually a flap of soft tissue on top of them, and during inspiration they prolapse, with a sliding forward movement, into the glottic opening, and vibrate with their flaps causing a rattle. I have seen a number of such babies and on one occasion removed the soft tissue flaps immediately curing the stridor.

These abnormalities are illustrated in Fig. 2.

In the last three or four years I have come across eight babies whose stridor has not been due to these developmental abnormalities which disappear as the baby grows older, but to localized conditions open to surgical remedy, and if not so treated likely to be fatal. Four of the babies each had a cyst in or close to the larynx, two a haemangioma in the lower part of the larynx, one a cleft larynx and one a foreign body in the larynx. As a result of these experiences, I believe it is advisable to examine the larynx of all babies with laryngeal stridor. There may be circumstances in which the services of expert laryngologists and anaesthetists are not available. Then it might be wiser and safer to observe the infant with stridor over a period of weeks or months, provided the signs and symptoms conform to the well known pattern of inspiratory laryngeal collapse and there is a tendency to improvement, with no attacks of cyanosis or dyspnoea.

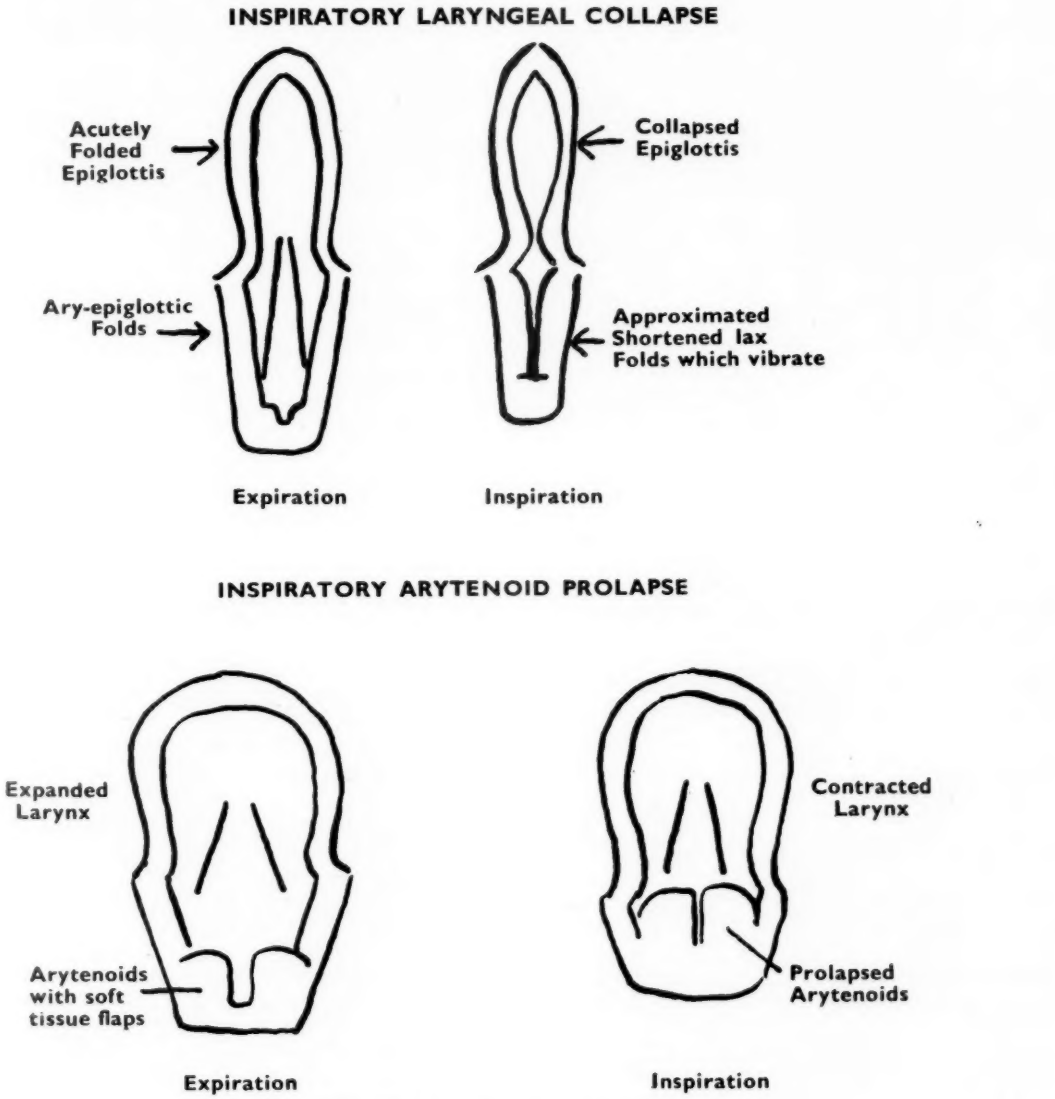

FIG. 2.—Types of infantile larynx causing stridor.

Cysts Causing Stridor

Fig. 3 is a drawing showing the position of these cysts, two in the ary-epiglottic fold, one derived from the ventricle of the larynx and one lying on the back of the tongue and causing obstruction of the laryngeal aperture.

Ary-epiglottic Fold Cysts.—One was in a boy who had difficulty in breathing from birth and was nursed in an oxygen tent for stridor and cyanosis. He had to have tracheotomy at 14 days old at his local hospital, and at 3 weeks old the surgeon there could see that the right ary-epiglottic fold was thick. At 2 months old I could see that there was a cyst in the fold and aspirated clear fluid from it. I removed a piece of the cyst then and upon two subsequent occasions. It was lined with pseudo-stratified columnar ciliated epithelium. At 4 months old there was a reasonably good aperture to the larynx, the tracheotomy tube was removed and the baby went home. After two months at home he developed laryngo-tracheitis with spasm and a tracheotomy was made and he returned to my ward. The trachea above the tracheostomy collapsed, and although he had a good laryngeal aperture after the laryngitis settled, it took 18 months and the same number of operations, including splinting the upper trachea open with a wire bridge, before he could breathe without the tube. At 4½ years he was strong and well with a good voice.

The other ary-epiglottic cyst was also in a boy, aged 2 months, who was admitted to my ward at the request of Dr. George Newns. He had had stridor since birth, causing indrawing of the ribs, and increasing progressively. Feeding had become more and more difficult. He developed an upper respiratory infection five days before admission (there were colds in the family), and his difficulty in breathing had become worse in these days. The diagnosis on admission was inspiratory laryngeal collapse, with superadded laryngitis, but the physician suspected that there might be another abnormality of the larynx. The baby was given oxygen and aureomycin, and his condition was maintained. Four days later laryngoscopy was performed under general anaesthesia, and a rounded cyst was seen occluding the anterior half of the laryngeal opening, superficial to the cords. Its origin could not be determined, but as much as possible of the cyst was seized in biting forceps and removed. The bleeding was not great, and breathing was immediately easier. The blood was sucked out repeatedly during the next few hours while the baby lay in the theatre with all hands standing by. He settled into quiet respiration, and thereafter made uneventful progress, taking his feeds well. He left hospital in a week, and the larynx was examined a month later. It was normal but for a small

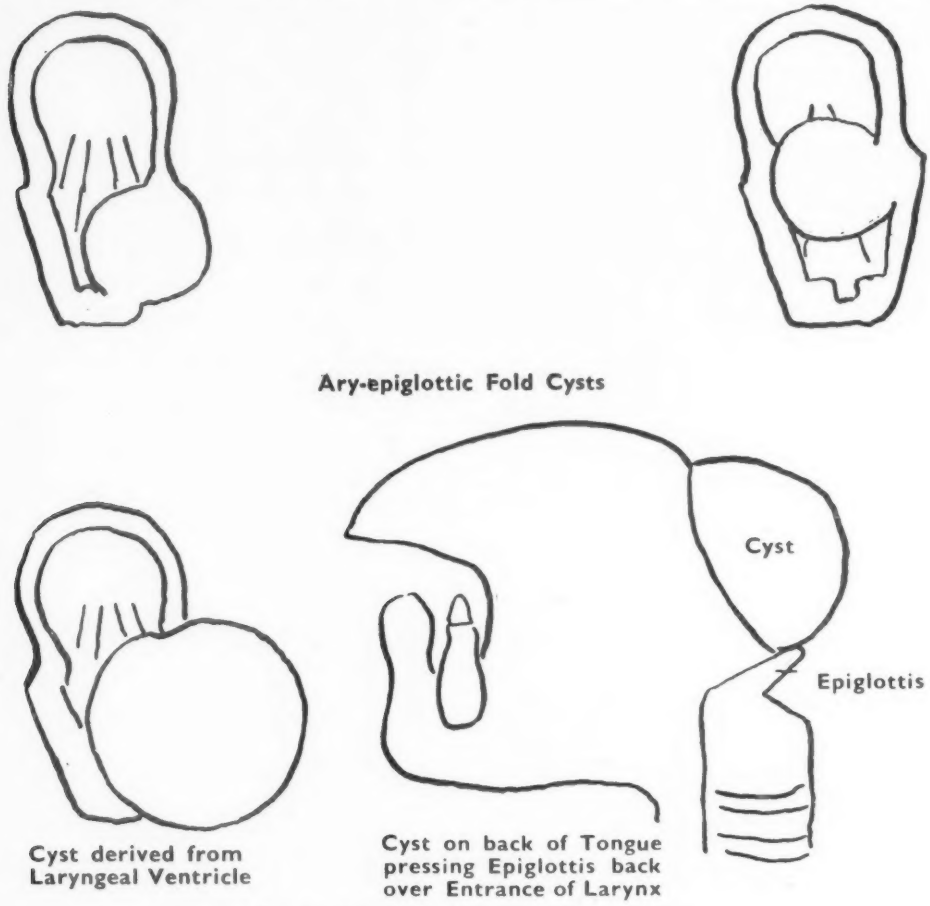

FIG. 3.—Cysts causing laryngeal stridor in infants.

raised pink scar at the junction of the right ary-epiglottic fold with the epiglottis. Section showed the cyst to be lined with flattened respiratory columnar epithelium, and covered with squamous epithelium, presumably derived from that of the epiglottis. This ary-epiglottic fold cyst had been removed, fortunately and almost completely, at one operation without tracheotomy. The baby enjoyed great advantages over others who had to overcome the dangers of tracheotomy with collapse of the upper trachea and many operations and a prolonged stay in hospital.

In a following paragraph the troubles of tracheostomy in very young babies are discussed.

Cyst Derived from the Laryngeal Ventricle.—This type of cyst was in a baby girl 1 year old under the care of my colleague Mr. Henry Sharp. She was in hospital with pylorospasm, and was found to have laryngeal stridor which rapidly became worse, so that after two weeks tracheotomy was necessary. A large thin-walled cyst was found to rise up from the side of the larynx and overlap its entrance. Thin grey fluid was aspirated and a large part of the cyst wall removed; it was lined with stratified squamous epithelium. Thereafter the aperture of the larynx looked adequate, but the baby could not be brought to breathe through it because the trachea above the tracheotomy tube collapsed. She died a few weeks later during an operative procedure.

These three cysts are representative of the usual type of cyst found in the infant larynx. Ahlén and Ranström (1944) report one and refer to 20 others, and Holinger and Steinmann (1947) report two. With the three described here there are 26 laryngeal cysts in the infant on record, and 17 died. Theoretically they were all open to surgical cure.

Thyro-glossal Duct Cyst.—This cyst was not in the larynx itself, but on the back of the tongue and compressed the larynx causing stridor. It also caused difficulty in feeding and it was for this reason that the baby girl of 6 weeks came into hospital. The physician looking after her, Dr. Wilfrid Sheldon, put his finger in her mouth and remarked that there was not enough room low down in the pharynx for her to swallow easily, and he thought that there must be a cyst there. I saw a large thin-walled cyst, and aspirated some fluid which digested starch. A large piece of cyst wall was removed and section showed it to be lined with stratified squamous epithelium with a few acini of salivary glands in the connective tissue. It was thought to be the dilated upper end of the thyro-glossal duct. After the operation the baby made rapid progress, with easy feeding and no stridor.

Haemangiomata Causing Stridor

Both of the patients with haemangiomata were boys who developed inspiratory stridor at about 3 months of age. The one who died had attended a hospital where a diagnosis of 'congenital laryngeal stridor' had been made, and the mother told that 'he had a small larynx and would grow out of his trouble.' But he did not. He got worse, and when Dr. P. R. Evans saw the baby he noted that the stridor did not improve when he pulled the tongue forward, and that there were several haemangiomata on the skin, and wrote in his out-patient notes: 'there might be a laryngeal angioma or something of that sort.' On laryngoscopy and bronchoscopy a rounded swelling was seen protruding from a broad base on the posterior wall of the larynx about a quarter of an inch below the vocal cords. The airway was narrow but had proved to be

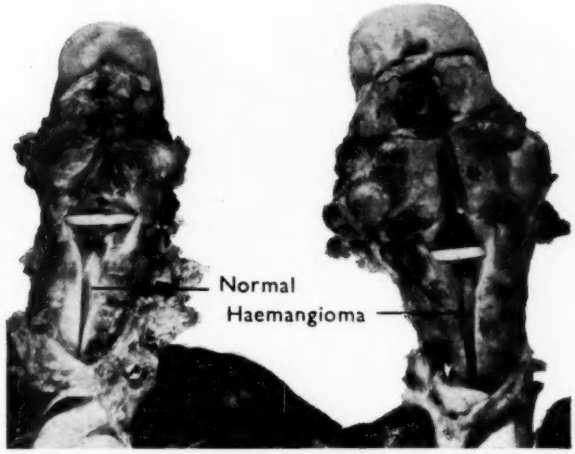

FIG. 4.—On the left normal baby's larynx, split from the front. On the right a haemangiomatous tumour protruding into the lumen from the posterior wall of larynx and upper trachea.

adequate so far. Impressed with the difficulties I had experienced with the other similar baby, I decided to treat this haemangioma by x rays and the child went back to the medical ward. He died 36 hours later. Figs. 4, 5 and 6 show this tumour.

The other baby boy came to us at 4½ months from another hospital for investigation, having had inspiratory

FIG. 5.—Haemangioma of posterior wall of larynx and upper trachea on section.

stridor and attacks of pallor since he was 3 months old. The laryngoscope and bronchoscope showed a rounded swelling on the posterior wall of the larynx about half an inch below the vocal cords. A tracheotomy was made and a fortnight later the larynx was split by laryngo-fissure operation and the rounded tumour, which was faintly blue, was cut out. The larynx was sewn up and the baby recovered from the operation well. Section of the tumour showed it to be a capillary haemangioma with very few formed vessels. It was not possible to get the baby to breathe through the larynx, because yet again the trachea above the tracheotomy collapsed. In addition, three months later, the angioma became evident again. He was given two treatments by deep x ray at four months' interval, but it was not until he was 15 months old that we were able to get him to breathe through the larynx. He has been very well for the last year, and a recent examination showed only a small pale raised scar, with a good airway.

Suehs and Herbut (1940) describe one and refer to seven other examples of haemangioma in the infant larynx, and Ferguson (1944) records one. With these two added there are 11, of whom five recovered.

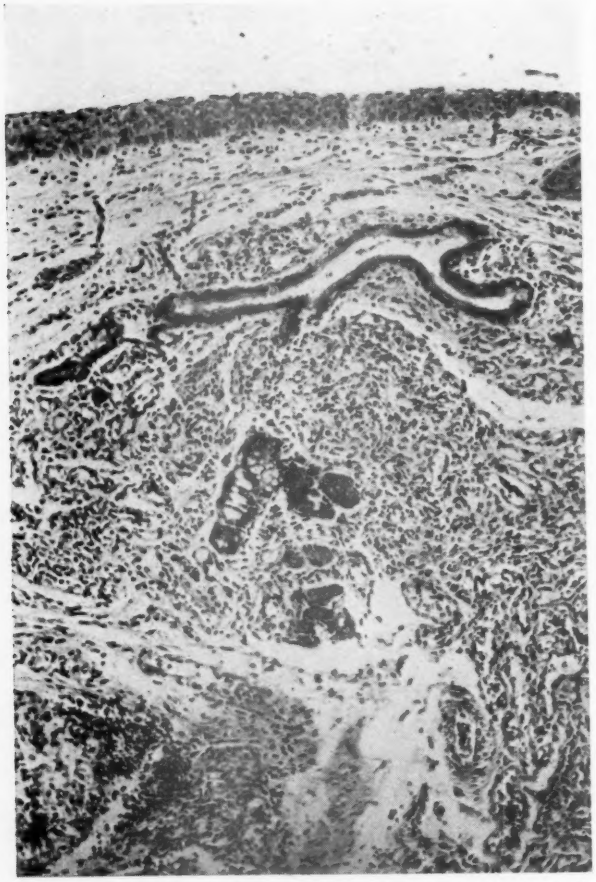

FIG. 6.—Haemangioma of larynx × 75. Numerous endothelial cells and few blood spaces.

Cleft Larynx Causing Stridor

The cleft larynx baby was a member of a family of five children, the first four of whom were described by Finlay (1949). Three of her sisters died in the same sort of way as she did, at about 3 or 4 months old, from ulcerative tracheitis or infection of the lungs. I examined the larynx of this baby girl when she was 3 months old and in hospital under Dr. George Newns for inspiratory stridor and feeding difficulty. I did not notice the cleft between the arytenoids. It seemed to me to be a larynx of the 'inspiratory laryngeal collapse' type. But at necropsy Dr. M. Bodian found a cleft between the arytenoids. Finlay had noticed a cleft in one of the sisters and it seems that the two others who died probably also had clefts.

FIG. 7.—Cleft in posterior wall of larynx between arytenoids.

I believe Dr. Bodian has found two other examples of what he calls 'cleft larynx' apart from the members of this family. Now that one is aware that such a condition exists, a careful inspection of that part of the larynx on laryngoscopy should, sooner or later, enable a diagnosis to be made during life. Then perhaps oesophageal feeds will prevent the fatal consequences of food getting into the lungs, and a baby may reach a size when surgical repair of the cleft is possible.

Foreign Body causing Stridor

My last example of non-inflammatory laryngeal stridor is a very obvious one, after the event. But this baby boy of 11 months had a cold for a few days, developed sudden stridor and difficulty in breathing, and was taken to a London teaching hospital where a diagnosis of laryngo-tracheo-bronchitis was made. There was not a cot for him so he was transferred to The Hospital for Sick Children with that diagnosis, which set our admission officer off on the wrong foot. An accurate history might have corrected the error, but the parents were Italian with very little English, and our admission officer English with very little Italian. Laryngoscopy of this baby with very severe respiratory difficulty and laryngeal stridor, in the early hours of the morning, revealed a large piece of bone jammed between the vocal cords, and there was a rapid recovery after it was removed. The necropsy was not upon the child, but upon the history of his illness, when it was elicited that the attack of respiratory difficulty had

come on suddenly when the baby was drinking soup—Italian soup with bone in it.

These examples are from the writer's own experience in the last few years, but they do not cover all the causes of laryngeal stridor in infants. For instance, a considerable number of cases of webs in the infant larynx have been described.

Tracheostomy in Young Infants

Tracheostomy tubes had to be kept in position in two of the babies here described for a year and a half before they could be removed although the original cause of the laryngeal obstruction, which had necessitated the tracheostomy, had been overcome in the first few months. A third baby died during an operative procedure to overcome tracheal obstruction following tracheostomy.

The trachea of an infant up to a few months old collapses above a tracheostomy if the tube is kept in for more than a few days. This seems to be due to loss of strength of the trachea after one or two of its soft rings have been divided, and to the negative pressure in the larynx and upper trachea which is present during inspiration (Fig. 1). This negative pressure is less above the tracheostomy than below, but the tracheotomy tube props open the lower trachea. The collapse of the upper trachea prevents the baby from resuming normal breathing even when the larynx itself has a good lumen. In two of the babies described here, numerous operations, and various modifications of tracheotomy tube, including varieties with a tube passing up as well as down, failed to hold the collapsed upper trachea open. The passage of time and growth of the child eventually succeeded where all our efforts had failed. The trachea enlarges and the rings become firmer. There is also a very important mental element. The baby finds it easy to breathe through the tracheotomy tube, and seems to lose the natural ability or inclination to breathe through the larynx. When he is about a year and a half old it is possible to educate him to breathe through the larynx again by taking out the tube for short periods, and blocking the tracheostomy with the finger. At this stage it may be possible to dispense with the tube, with the tracheostomy closed, for hours or days at a time if the baby is put in an oxygen tent, whereas in ordinary air he becomes cyanosed. The lesson that has been learnt from all this is that a tracheotomy tube should only remain in a young baby for a very few days if at all possible. For instance a tracheostomy should not be made and at a subsequent date the obstruction in the larynx removed. Both should be done at the same time. It is better still to remove the laryngeal abnormality without a tracheostomy. The last of the ary-epiglottic cysts displays the enormous advantages to the baby if this can be done. He was only a week in hospital, and had only one operation compared with 18 months in hospital and a similar number of operations suffered by the other ary-epiglottic cyst case which had a tracheostomy. The one operation of the fortunate baby required great skill and experience on the part of the anaesthetist at least. A general anaesthetic is necessary to examine or operate on an infant's larynx, and this baby with laryngeal obstruction and cyanosis came straight out of an oxygen tent to the theatre. The operation was followed by some anxious moments during the recovery period when the baby lay in the theatre with everyone in attendance. He left hospital in a week and when seen a month later was in every respect a normal baby.

Summary

'Congenital laryngeal stridor' is a clinical description and should not be used to denote the specific entity of inspiratory laryngeal collapse of infants. This condition is described, and also another developmental abnormality the baby outgrows, which the writer calls inspiratory arytenoid prolapse.

Case records are given of eight babies with laryngeal stridor due to localized conditions in the larynx open to surgical treatment, and if not so treated likely to prove fatal. Four of the babies had a cyst, two a haemangioma, one a cleft larynx and one a foreign body.

The literature reveals a high mortality in similar cases.

The larynx of a baby with stridor should be inspected to establish the cause.

The difficulties and dangers of tracheostomy in young infants are discussed.

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A CASE OF PHAEOCHROMOCYTOMA IN CHILDHOOD

BY

M. ISRAELSKI, A. C. KENDALL and R. E. SHAW

From the George Eliot Hospital, Nuneaton

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A sufficient number of cases of phaeochromocytoma have now been described for the clinical features they present to be clearly defined. Once the diagnosis has been suspected, other conditions associated with hypertension in childhood can usually be excluded on clinical grounds. Confirmation may then be sought by means of the benzodioxane test (Goldenberg, Snyder and Aranow, 1947) and the more recently described assay of noradrenaline in the urine (von Euler, 1951). Operative treatment is aided considerably by pre-operative localization of the tumour, using the technique of extra-peritoneal pneumography, a method of investigation which appears to be free from the dangers associated with perirenal air insufflation. Lastly, the hazards associated with the operation itself can be reduced considerably by the use of benzodioxane. These means were used successfully in the case to be described.

Case Report

A boy aged 10 years presented with a nine months' history of loss of weight, 5 lb. being lost in the last six months, listlessness, excessive sweating, particularly at night and after exertion, increasing thirst and polyuria. For one month he had complained of frontal headaches which were worse on rising and he had vomited on three occasions. His mother's anxiety was increased by the fact that the boy's father had died at the age of 23 years after an illness presenting similar features. He had, she related, from the age of 16 years sweated excessively, but until six months before his death seemed well. Some impairment of vision was then complained of, he was found to have slight papilloedema, a blood pressure of 210/170 mm. Hg, and albumin, red cells and cellular casts were present in the urine. His death was apparently due to a cerebral catastrophe, but no necropsy was done.

The patient was normally proportioned for his age, although rather thin (height, 55 in., weight, 68½ lb.). Puberty changes had not begun. He had a pale face, an anxious expression and manner, his skin was moist and there were beads of sweat on his forehead. Over the hands and wrists there was a dull red flush, the upper limit of this change showing a sharp line of demarcation. Similar but less marked changes were present in the feet and ankles. The heart was not enlarged, the heart sounds were normal apart from an accentuated second sound in the aortic area, and there were no murmurs. His blood pressure was 200 mm. systolic and 150 mm. diastolic. Both fundi showed early papilloedema and an exudate in the form of a macular fan. There were no other abnormal findings.

Following admission to the ward his pulse rate was found to vary between 80 and 120 per minute but was mostly in the range of 80 to 100. His skin was always moist and invariably during sleep sweating was profuse. The blood pressure showed marked spontaneous variation, the highest reading obtained being 250 mm. systolic and 180 mm. diastolic and at that time he perspired profusely and complained of severe frontal headache. His fluid intake varied from 3 to 5 pints a day.

Special Investigations.—Several specimens of urine were normal. A concentration test gave a specific gravity of 1020. Urea clearance in the first hour was 96%, and in the second 73%. The blood urea level was 42 mg. per 100 ml. Analysis of the plasma proteins gave albumin 4·6 g. per 100 ml., globulin 2·2 g. per 100 ml.

A radiograph of the chest showed a normal cardiac outline.

Benzodioxane Test.—An intravenous drip of normal saline was started, and blood pressure readings were taken at minute intervals. Spontaneous fluctuations were seen (Fig. 1), but by the end of the seventh minute when stabilization seemed to be occurring, a visitor came and announced to the boy that his vicar had called to see him. There was an immediate rise in the systolic and diastolic pressures, and thereafter increased fluctuations about a generally higher level. When these fluctuations had diminished, 11 mg. of benzodioxane were injected over a period of two minutes. The systolic pressure immediately fell by 65 mm., the diastolic pressure by 60 mm., and this was followed by a steady rise, the pre-injection levels being reached by the end of 10 minutes.

Nor-Adrenaline Excretion.—This was at the rate of 2,000 μg. in 24 hours. The normal limits for a boy of this age are 10μg. to 27 μg., average 20 μg.

Excretory Urogram.—There was good excretion from both kidneys. The right kidney shadow was somewhat larger than the left, and the upper pole of the right renal pelvis was slightly depressed (Fig. 2).

Extra-Peritoneal Pneumography.—This procedure was carried out according to the technique described by Blackwood (1951). Morphine, grain ⅛, was given half an

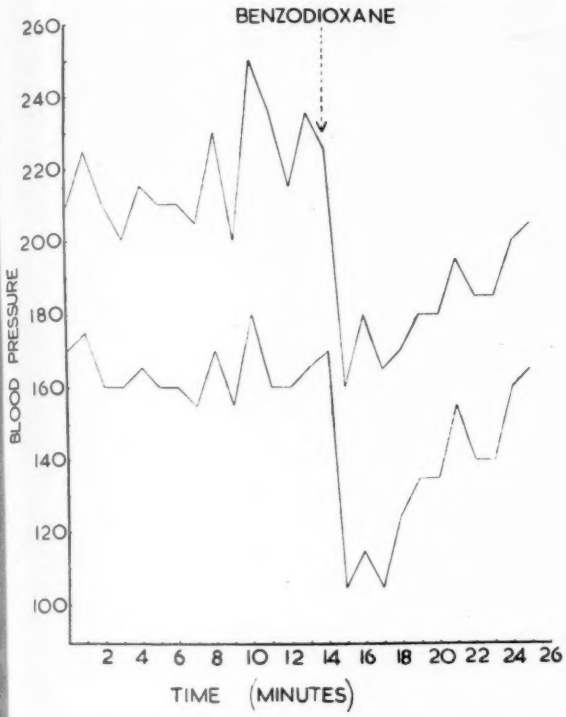

FIG. 1.—Results of benzodioxane test.

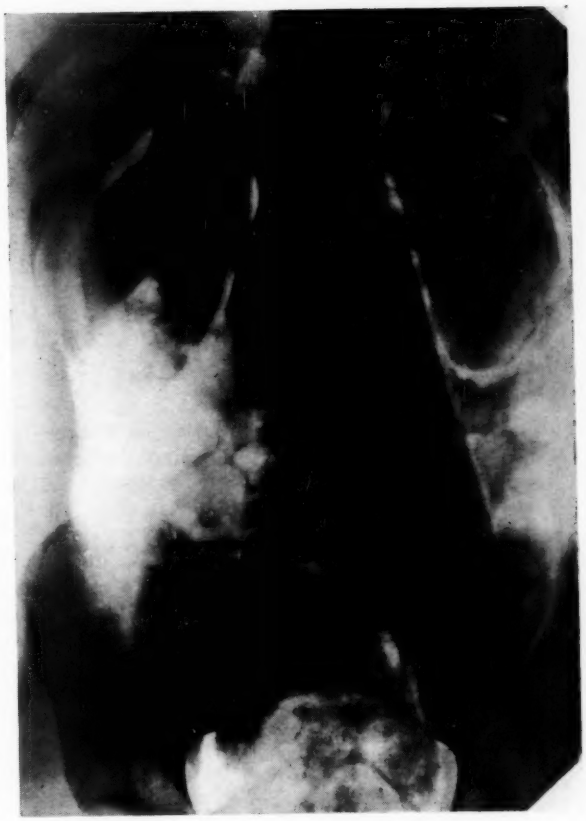

FIG. 3.—Extraperitoneal pneumogram.

FIG. 2.—Urogram of excretion.

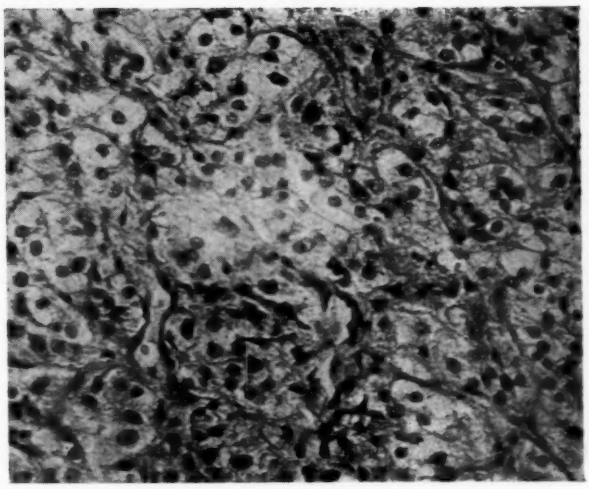

FIG. 4.—Section of tumour. ×400.

hour before, and blood pressure readings were taken at frequent intervals throughout the procedure. With the patient in the left lateral position, 400 ml. of air was injected; he was then placed in the right lateral position and a further 400 ml. injected. An x-ray picture taken immediately showed surgical emphysema to be limited to the pelvis. After the boy had walked about slowly for five minutes a further film showed the air to have reached the underside of the diaphragm and the kidneys and a tumour at the upper pole of the right kidney was clearly outlined. The left suprarenal shadow was normal (Fig. 3). During the whole of the procedure the boy's only complaint was of slight abdominal discomfort. His blood pressure, initially 180/150 mm. Hg, rose to 200/170 then fell spontaneously to 150/110.

Operation on March 2, 1953.—With the patient lying on his left side, the right kidney was approached through an oblique incision in the right loin. The incision crossed the last rib, the outer half of which was resected. A small hole accidentally made in the pleura was repaired. The kidney was exposed and then pulled downwards by a retractor held by the assistant; the tumour at its upper pole came into view. With a minimum of manipulation, the tumour was gently separated from the surrounding fatty tissue, which was very vascular. The line of demarcation was clear and apart from persistent oozing of blood from the fat, the removal of the tumour was easy. At the medial side of the tumour a large vein of the dimensions of a lead pencil passed to the inferior vena cava. This vessel was carefully divided between ligatures. Some yellow tissue seen in the bed of the tumour appeared to be normal suprarenal tissue. The wound was closed without drainage after complete haemostasis had been established. A chest radiograph taken at the conclusion of the operation showed no pneumothorax.

Anaesthesia and Management during Operation.—The anaesthetic was given by Dr. E. S. M. Merry. After premedication with omnopon, gr. $\frac{1}{6}$, and scopolamine, gr. $\frac{1}{300}$, anaesthesia was induced with intravenous thiopentone, 0·2 g., and continued with nitrous oxide and oxygen. Tubarine, 8 mg., was then given intravenously and a cuffed endotracheal tube inserted. Throughout the operation nitrous oxide, oxygen and minimal amounts of ether were given.

It was planned to prevent the systolic blood pressure from rising above 200 mm. by the use of benzodioxane intravenously; accordingly the first step was to begin an intravenous infusion with dextrose saline. In practice, fluctuations in the blood pressure occurred so rapidly, particularly during the first stage of anaesthesia, that isolated readings above this figure were obtained, the highest reading being 230 mm. During the course of the operation benzodioxane was injected on eight occasions, a total of 54 mg. being given.

After the efferent vein had been clamped nor-adrenaline was infused at a rate of 6 μg. per minute. The blood pressure remained constant between 100 and 115 systolic and 65 and 80 diastolic, so that after two hours the rate of infusion was gradually reduced, the infusion being finally discontinued five hours after operation.

Pathology of the Tumour.—The tumour, brownish red and ovoid, measured 2 in. × 1½ in. × 1¼ in. Microscopically it had the appearances of a typical phaeochromocytoma with no evidence of malignancy (Fig. 4).

Nor-adrenaline was isolated from the tumour.

Post-operative Course.—The boy's blood pressure has remained in the range of 105 to 125 systolic and 75 to 85 diastolic, he no longer sweats excessively, and he has had no headaches. During the two months since the operation he has gained 10¼ lb., and has lost his anxious and drawn expression. The fundi still show star figures in the macular regions, but the discs themselves are normal.

Discussion

The symptoms associated with phaeochromocytoma may be paroxysmal at first and later sustained, or, sustained from the onset. Although this boy had no dramatic crises, his symptoms showed great variation in degree, but at no time was he symptom free. Similarly his blood pressure, while being persistently raised, showed a marked lability, not only from day to day but frequently from minute to minute. This variation in the blood pressure during the stage of persistent hypertension was a feature of the cases reported by Hubble (1951) and by Neill and Smith (1952).

The benzodioxane test was positive, supporting the clinical diagnosis. The great value of this test is now recognized, although negative results in proved cases of phaeochromocytoma and positive results in their absence have been described. Tulloh (1952), reported an example of a false negative test, and, reviewing previously reported similar cases, considered the factors which may have been responsible. False positive results appear to be even less frequent, but may occur in the presence of adrenal medullary hyperplasia (Taliaferro, Adams and Haag, 1949). One may conclude with Hubble that the benzodioxane test, although not completely reliable, 'has a degree of specificity unusual in most clinical or laboratory diagnostic tests'.

The demonstration of an increased urinary excretion of nor-adrenaline is the most convincing evidence of the presence of a phaeochromocytoma. In our patient 2,000 μg. was excreted in 24 hours, a level which is 100 times the average value. Dr. G. P. Burn (personal communication) pointed out that the nor-adrenaline urinary excretion has to be correlated with the clinical state of the patient and the blood pressure levels during the period over which the specimen is being collected. In patients with paroxysmal attacks the urinary nor-adrenaline level is likely to be significantly raised only during attacks and to be normal during the asymptomatic periods.

Retro-peritoneal pneumography was used to localize the tumour. This method of investigation,

first introduced by Ruiz Rivas (1950), consists in the production of a retro-peritoneal emphysema by the injection of air into the pre-sacral areolar tissue. As this area is poorly vascularized the procedure appears to be devoid of the risk of air embolism, a disaster which has brought perirenal air insufflation into discredit. Steinbach, Lyon, Smith and Miller (1952) quote Ruiz Rivas as stating that L. P. Mosca has collected 1,500 cases of extra-peritoneal pneumography including 220 of his own without any fatal complications. Accurate pre-operative localization of the tumour is of great assistance in planning the operation, and in the case of our patient allowed an approach through the loin to be made instead of by the more difficult transperitoneal route. This latter route is advocated by Sprague, Kvale and Priestley (1953) on the grounds that pre-operative localization of the tumour is often impossible, and also because multiple and bilateral tumours may be present. While it is true that multiple tumours may be present, Mac Keith (1944) states that 'the common lesion is a benign adenoma of one adrenal body', and of 152 cases he reviewed, in all but 16 a single tumour was present. Retro-peritoneal pneumography in the case of our patient gave the added and valuable information that the contralateral supra-renal appeared normal.

The chief hazard of operative procedures of any kind, and particularly of those which involve manipulation of the tumour, is that hypertensive crises may occur as a result of the discharge of nor-adrenaline into the circulation. Such crises are liable to be followed by a state of severe and often fatal peripheral circulatory collapse. It is important therefore that at operation the tumour should be disturbed as little as possible until the efferent vein has been ligated, and also that an adrenolytic agent should be held ready for immediate injection. For this purpose benzodioxane, which has a transient action, is to be preferred to dibenamine, the effects of which are similar but persist for two or three days. If dibenamine were to be used, it would, by its more prolonged action, prevent the use of nor-adrenaline should it be required to correct a post-operative fall in blood pressure.

Summary

A case of phaeochromocytoma in a boy aged 10 years is described. The benzodioxane test was positive and the urinary excretion of nor-adrenaline was markedly raised.

Retro-peritoneal pneumography demonstrated the tumour, which was successfully removed.

We are grateful to Dr. G. P. Burn for his advice and for carrying out the nor-adrenaline estimation, to Dr. McCullagh Wilson for his report on the pathology of the tumour, to Mr. Partridge for the photographs. Dr. Joyce, the paediatric house physician, rendered invaluable assistance.

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HORMONAL SEX REVERSAL IN A FEMALE

BY

W. J. MATHESON and E. M. WARD

From the Children's Hospital and Pathological Department, Leicester Royal Infirmary

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The terms pseudo-hermaphroditism and hermaphroditism have been used in different senses by various authors and for this reason they were discarded by Wilkins (1950). He describes as 'intersexes' (hermaphrodites) those cases in which the sexual dimorphism is not due to a demonstrable endocrine abnormality, and as cases of 'sex reversal' those in which there is an endocrine abnormality.

Hormonal sex reversal in the female due to congenital adrenal hyperplasia is not infrequent and is probably the commonest cause of heterosexual development (Wilkins, 1950). In most cases virilization does not start until after the external genitalia have practically completed their normal female differentiation and the anatomical abnormality is fairly uniform. Cases similar to that to be described, in which virilization appears to have started at an earlier stage of development, are most unusual and in fact only two are on record (Wilkins, quoting an unpublished case of Reilly, 1950; Schiller, 1940).

Case Report

P.C. was 10 days old on admission to the Children's Hospital, Leicester Royal Infirmary, on January 9, 1952. There had been persistent vomiting and loss of weight since birth. 'He' was the fourth child of healthy, unrelated parents born at term after an uneventful pregnancy. The infant weighed 8¼ lb. at birth. Of the siblings only a girl aged 10 years is alive; she has been examined and found to be a normal, healthy girl. Two brothers died in infancy, the first when he was 8 months old in another hospital. He had never thrived and vomited frequently. It has not been possible to obtain any further information about him but the mother states that all her 'boys' had the same symptoms and that 'they have all gone the same way'. The second brother died in the Leicester Royal Infirmary at the age of 4 weeks; he also suffered from persistent vomiting and loss of weight. On the day before death alkali reserve was 40 volumes % and serum chlorides 88 mEq. per litre. At necropsy no cause of death other than bronchopneumonia was found. Idiopathic renal acidosis had been considered as a possible diagnosis but the biochemical findings did not support this and no calcification was found in the renal tubules.

On admission P.C.'s temperature was 99° F., pulse rate 140 and respirations 36 per minute. Weight was 6 lb. 13 oz. Apart from signs of loss of weight and dehydration, no other definite abnormality was found except that the penis appeared large for the child's age.

Urine was tested on January 8 and January 11 when a small amount of protein was found. A chromatogram (Dr. Bickel) on January 24 showed no abnormal excretion of amino-acids, but traces of fructose and lactose. A specimen of urine on February 4 showed no cystine crystals, but glucosazone was obtained. Serum chlorides on January 12 were 90 mEq. per litre; on January 22, 98 mEq.; and on February 4, 55 mEq.

Tests for blood urea on January 12 gave 64 mg. % and 80 mg. % on February 4.

An intramuscular pyelogram on January 15 was abandoned because the kidney was obscured by gas in the intestine on a straight film.

Feeds were taken fairly well but there was little gain in weight which fluctuated between extremes of 7 and 6¼ lb. The baby vomited at least once or twice a day and dehydration, frequently out of proportion to the vomiting, necessitated the administration of normal saline subcutaneously in amounts of 4 oz. once or twice daily. Terminally there were signs of bronchopneumonia: The infant died on February 10, 1952, at the age of 6 weeks.

Apart from the parenteral saline, DOCA was given daily intramuscularly in doses of 2 mg. from February 4 without apparent benefit.

Originally a diagnosis of an inborn error of metabolism was considered, but Fanconi's syndrome was suggested by the finding of albuminuria and glycosuria although there was no abnormal excretion of amino-acids. Serum chloride levels were not at first considered to be sufficiently low to justify a diagnosis of adrenal cortical hyperplasia with insufficiency (blood samples taken for potassium estimation were unfortunately haemolysed) but latterly there was a considerable fall and this was the final clinical diagnosis; the glycosuria found was probably due to the adrenal dysfunction.

Necropsy Report.—The body was that of a very emaciated infant. The external genitalia appeared to be those of a normal male; the external urinary meatus opened at the tip of the glans and the scrotum was normal in size and appearance but contained no testes (Figs. 1 and 2). In the abdomen both adrenal glands were very large, weighing together 18 g. There was a well

formed uterus lying in its normal position with Fallopian tubes, ovaries and round ligaments on each side. The uterine cervix was of normal appearance and the upper four-fifths of the vagina well formed and of normal calibre; the lower fifth was very narrow and would only admit a probe which passed through to open into the

FIG. 1.—Post-mortem photograph of abdominal viscera.

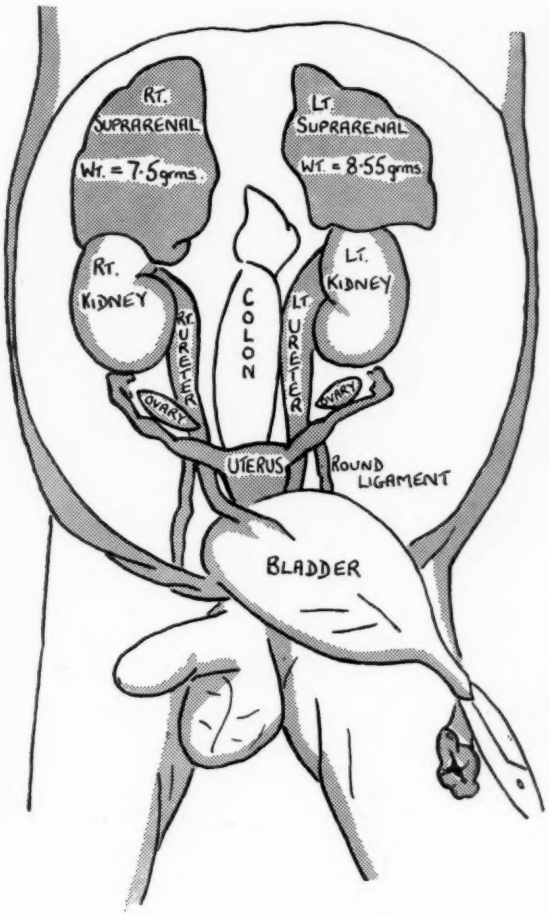

FIG. 2.—Diagrammatic representation of Fig. 1.

posterior urethra at the verumontanum (Fig. 3). In the angle between the superior surface of the vagina and the posterior surface of the urethra lay a prostate.

There was bilateral hydro-ureter, more marked on the left than the right. There were well marked mucosal valves in the posterior urethra below the verumontanum and the bladder was hypertrophied.

There was bronchopneumonia of both lungs.

ADRENAL GLAND. Microscopically the zona glomerulosa is very thin, consisting only of two or three rows of compressed cells. The zona fasciculata is well shown but the main mass of the cortex consists of a zona reticularis (Fig. 4). In the fuchsin-stained section (Fig. 5) most of the cells of the zona reticularis are stained deeply.

PENIS. Cross-section shows the urethra lying in the centre of the corpus spongiosum with the joined corpora spongiosa above.

OVARY. There are a large number of tiny graafian follicles but others are developing and show well marked discus proligerus. The largest is 8 mm. in cross section in the fixed specimen (Fig. 6).

PROSTATE. The acini are small and are lined by a

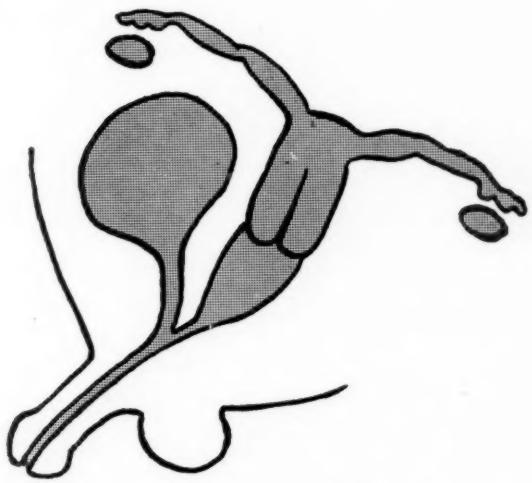

FIG. 3.—Diagrammatic cross-section to show relationship of vagina and urethra.

FIG. 4.—Section of adrenal cortex (haematoxylin and eosin × 90) showing narrow band of zona glomerulosa and wide bands of zona fasciculata and reticularis.

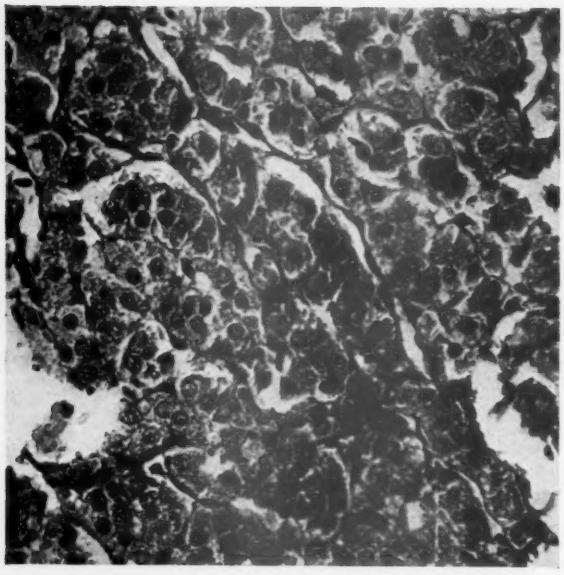

FIG. 5.—Section of adrenal cortex (Ponceau-fuchsin × 235) showing the darkly stained granules in the cells of the zona reticularis.

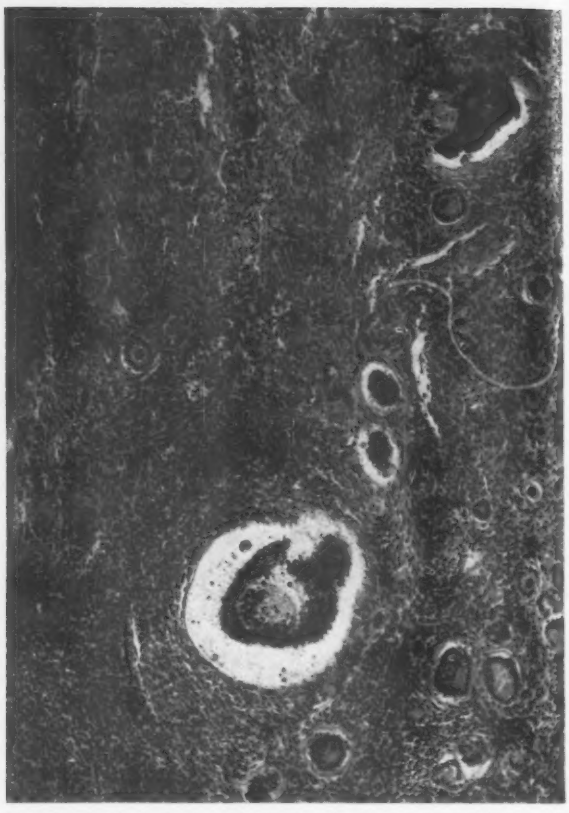

FIG. 6.—Section of ovary (haematoxylin and eosin × 90) showing large number of undeveloped and several developing follicles.

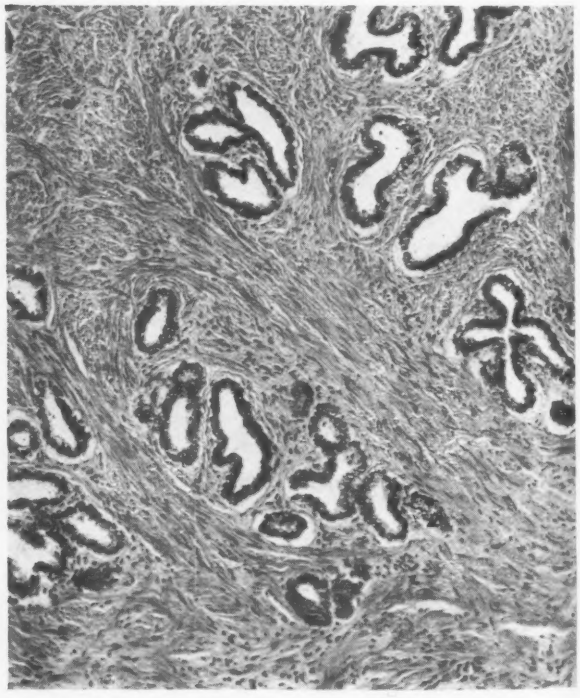

FIG. 7.—Section of prostate (haematoxylin and eosin × 90) showing normal architecture of the gland.

double row of cubical epithelium; they lie in a musculofibrous stroma. No corpora amylacea can be identified (Fig. 7).

Discussion

The human embryo is potentially bisexual up to about the 25 mm. crown-rump stage (52 days) when the primitive gonad develops into a testis or ovary (Hamilton, Boyd and Mossman, 1952). Even for some time after this male and female development follows similar lines; thus the para-mesonephric (Mullerian) duct system is identical in male and female up to the 27 mm. (54 days) stage and the development of the urethra in both sexes follows a similar pattern up to about the 38 mm. (65 days) stage. By about the 45 mm. stage (70 days) the male external genitalia reach approximately their final form, that is to say the urethral folds, which in the female become the labia minora, have fused as far as the glans to form the urethral tube. The labioscrotal swellings, however, do not finally fuse to form the scrotum until about the 55 mm. stage (77 days). The duct system is the last to reach its final form; the mesonephric (Wolffian) duct begins to degenerate in the female at about the 30 mm. stage but traces persist up to the 70 mm. stage and in some cases for longer. The para-mesonephric duct in the female is not fully differentiated until the 150 mm. stage (110 days) when the uterine portion of the utero-vaginal canal becomes separated from the vaginal; the urethral and vaginal orifices do not become separated finally until the 162 mm. stage (118 days).

Sex Determination.—It is generally agreed that sex is genetically determined and that hormones execute a pre-determined plan (Hoffman, 1944). When, however, each phase begins and ends is a matter of controversy. The two extreme views may be represented by, on the one hand, the belief that the gonads, ducts and external genitalia are entirely genetically determined (Moore, 1947) and that the function of hormones is to complete sexual maturity post-natally; on the other hand it is held by others that genetic influences determine whether the primitive gonad develops into a testis or ovary which then, by elaboration of hormones, influences further development along male or female lines (Greene, 1942). It is undeniable that sexual development can be influenced by hormones; this is seen in nature in the case of freemartins where the female twin is masculinized *in utero* by the male. Raynaud and Frilley (1947) destroyed the gonads of embryo mice aged 13 days by means of x rays and found that the development of females was unaffected but that males tended to develop along female lines. Similar results were obtained by Jost (1947) in the rabbit. It is suggested that, in the absence of embryonic testicular hormone, development proceeds along female lines through the influence of maternal oestrogen and, as a corollary, that the embryonic testis must produce sufficient hormone to counteract the effect of maternal oestrogen if the individual is to develop into a male (Wilkins, 1950). This hypothesis and the experiments on which it is based cannot be applied unreservedly to normal human development but it receives some support from two observations; first, that in the male a greater number of Leydig cells are present in the testis early in pregnancy when sexual development is taking place than later, and secondly that in ovarian agenesis the sexual characters are well defined (Schiller, 1940). The syndrome of ovarian agenesis could be used as an argument that sex is entirely genetically determined if a similar condition of testicular agenesis occurred in the male; such a condition, has, however, never been reported (Wilkins, 1950). The fact that sexual development can be influenced by hormones shows that embryonic tissues are responsive to them and makes it likely that hormones play a part in normal intrauterine development.

Sex of Present Case.—Of the two similar cases described, Wilkins (1950) considered his to be a female and Schiller (1940) his a male. We believe that our case was a female because the gonads were ovaries, the prostate was of female type (Young, 1937) and the anatomical pattern is explicable as that of a genetic female virilized.

But for the findings of large adrenals this case might be considered an 'intersex' due to a genetic aberration. Cases of feminization in the adult male due to adrenal tumours are described (Schiller, 1940) and it is arguable that this case could be a feminized male. No such case has, however, been described at this age, and according to Wilkins in all cases of sex reversal in which the gonads were ovaries there was evidence of excessive production of androgens.

In most cases of hormonal sex reversal in the female due to congenital adrenal hyperplasia the anatomical abnormality is fairly constant; the vaginal and urethral orifices are not separate but form a persistent urogenital sinus which opens below a hypertrophied clitoris resembling a hypospadic penis. The para-mesonephric duct system develops normally to form Fallopian tubes, uterus and vagina and the gonads are, of course, ovaries. This anatomical pattern suggests that the virilizing effects of the adrenal begin to exert an influence on development some time after about the 50 mm. stage when the external genitalia have undergone male or female

differentiation and before the 162 mm. stage when the urethral and vaginal orifices become separate (Wilkins, 1950).

Anatomically the interesting and unusual features of this case are the complete masculinization of the external genitalia, the presence of posterior urethral valves and of the prostate.

The External Genitalia.—The penis and scrotum were perfectly formed except that the scrotum contained no testicles. The urethra had a central terminal opening on the glans. The penis appeared to be larger than the average at this age (Fig. 1) and it is interesting to reflect that, had this child lived, she would have appeared externally to be a sexually precocious male.

Posterior Urethral Valves.—These were sufficiently well marked to cause urinary stasis. Higgins, Williams and Nash (1951) suggest that these valves are formed by excessive development and adhesion of the medial edges of the lateral submontal folds of mucous membrane which are seen normally from the 60 mm. stage onwards in the male. It is uncertain if they ever occur in the normal female in whom their presence would be inexplicable on embryological grounds since the female urethra corresponds only to the supramontal part of the urethra in the male.

Prostate.—The prostate consisted only of a middle lobe, i.e., it was related only to the 'supramontal' part of the urethra. In the male the prostate begins to develop at about the 55 mm. stage from buds which grow out of the urethra; the posterior lobe is derived from inframontal buds. In the female these urethral buds form the para-urethral glands and glands of Skene (Hamilton, Boyd and Mossman, 1952). In virilized females prostates may develop but there is never a posterior lobe (Young, 1937). This is to be expected on embryological grounds since the female urethra corresponds only to the supramontal part in the male, but it is surprising that the prostate was not fully developed in this case. The only explanation appears to be that genetic influences were sufficiently strong to prevent this. It is of interest that the male and female parts of the prostate maintain their differences in susceptibility to disease, since it is the posterior lobe which is more frequently involved in malignant disease and the middle lobe in prostatic hypertrophy (Young, 1937).

The adrenal cortex develops early and its growth is rapid so that it is already a relatively large structure by the 12 mm. stage. Since congenital adrenal hyperplasia is not infrequently found in more than one member of a family (Wilkins, 1950), and it is possible that the two brothers suffered from this condition, it seems likely that the adrenal cortex in this case was hyperplastic from the start and thus could exert a virilizing effect from the earliest possible moment. Virilization in this case began before the 45-50 mm. stage since the genitalia were of male form. Before this time, apart from the presence of a testis or ovary, the embryo is virtually bisexual.

Both brothers suffered from symptoms suggestive of adrenal insufficiency and it seems possible that they died, as the patient did, as a result. Cases of adrenal cortical hyperplasia with excessive production of androgens but diminished secretion of hormones controlling salt and water metabolism producing a picture like Addison's disease are well recognized and appear to be more common in the male than in the female; of 83 cases of hormonal sex reversal in the female only six showed signs of adrenal insufficiency, while of 16 cases of congenital adrenal hyperplasia in the male, 10 had symptoms of adrenal insufficiency (Wilkins, 1948). In neither brother was this diagnosis proved. The first died in another hospital and it has not been possible to obtain any details about him; the second died in this hospital, no convincing cause of death being found at necropsy. It is notoriously easy to overlook adrenal hyperplasia with insufficiency in the male; moreover the adrenals at 3 weeks (when he died) are normally large and pathological enlargement could thus easily pass unnoticed, particularly since they were neither weighed nor sectioned.

It may seem contradictory that virilization in this case was capable of altering the external genitalia to masculine but could not prevent the normal female differentiation of the para-mesonephric ducts. One possible explanation for this appears to be that the external genitalia are responsive to both testicular and adrenal androgen but that the para-mesonephric duct is only responsive to oestrogen or testosterone. If it is agreed that normal intra-uterine development is influenced by hormone secreted by the embryonic testis or ovary, it follows that the para-mesonephric duct system develops in the female under the influence of oestrogen and retrogresses in the male with testosterone; it has not, however, been postulated that it is responsive to adrenal androgen. The external genitalia, however, may be responsive to both adrenal and testicular androgen; in the adult female virilized by an adrenal tumour the external genitalia alone of the sexual organs are visibly altered. In this case the external genitalia might have been altered to the male form by adrenal androgen while the para-mesonephric duct system developed normally under the influence of oestrogen secreted by the ovary.

Summary

A case is described of congenital adrenal hyperplasia in which there were male external and female internal genitalia. The gonads were ovaries. There was a prostate and posterior urethral valves causing urinary stasis.

It is suggested that virilization began at a much earlier stage of development than is usual in hormonal sex reversal but that the para-mesonephric duct system developed normally because it is unresponsive to adrenal androgen.

We wish to thank Professor W. D. Newcomb and Dr. J. G. Bate for their help with the histology, Professor F. Goldby for his advice about the embryology, Dr. H. Jolly for advice and Mr. E. V. Willmott for the microphotographs.

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BLOOD SUGAR LEVELS IN BABIES BORN OF DIABETIC MOTHERS

BY

GEORGE M. KOMROWER

From St. Mary's Hospitals, Manchester, and the Department of Child Health of the University of Manchester

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Many observers have reported upon the blood sugar levels determined during the first days of life of normal infants; and it is generally agreed that there is considerable variation in the figures of different babies, and also some instability of the levels in each individual infant under investigation, the figures being invariably lower than those in older persons (Creery and Parkinson, 1953; Greenwald and Pennell, 1930; Hartmann and Jaudon, 1937; Ketteringham and Austin, 1938; McKittrick, 1940; Norval, Kennedy and Berkson, 1949; Smith, 1951; Wachter, 1949).

There is less information concerning the blood sugar levels of the infants born of diabetic mothers, but the evidence suggests an early and rapid fall to a low level followed by a slow rise to more normal levels (Haslewood and Strookman, 1939; Joslin, Root, White and Marble, 1952; Miller and Ross, 1940; Oakley, 1953; Pedersen, 1952; Peel and Oakley, 1950; Reis, DeCosta and Allweiss, 1950).

It has been possible to make some observations on 21 normal infants and 40 infants born of diabetic mothers, and figures are produced for comparison. Twenty-five of the 40 'diabetic' babies were given 50% glucose at set intervals during the first eight hours of life, a total of 2 g. of glucose being given in all, but no further feeding was attempted until the infants demanded. This regime, based on the work of Reis and his colleagues in Chicago (1950), was employed as part of an M.R.C. investigation into pregnancy in diabetes: the remainder were not given glucose and feeding was only begun when the infants cried hungrily.

The majority of the 'diabetic' babies were delivered by Caesarean section in the thirty-seventh to thirty-eighth week, the mothers being given 30 g. glucose within two hours of the operation.

Blood sugar estimations were made on the cord blood (umbilical vein), and on heel blood obtained at half hour, one hour, two hours, four hours, 12 hours and 24 hours. The method of estimation was a modification of the method employed by Haslewood and Strookman (1939), namely, 0·1 ml. of whole blood is pipetted into 3·70 ml. of isotonic sodium sulphate-copper sulphate solution in a conical centrifuge tube; 0·2 ml. of sodium tungstate is added, and the mixture is well shaken. The precipitated proteins and copper tungstate are spun down in the centrifuge; 0·5 ml. of the supernatant fluid (=0·0125 ml. blood) is mixed with 1 ml. of the mixed copper reagent in a ¾ in. diameter test-tube. The tube, stoppered with cotton wool, is placed in a boiling water-bath for exactly 10 minutes. After immediate cooling, 3 ml. of the phosphomolybdic acid reagent are added. The colour is compared with that produced by 1 ml. of a standard glucose solution in benzoic acid, treated in the same way as the blood filtrate. Duplicate readings were made as often as possible but as it was not feasible to obtain the full amount of blood on all occasions several of the results have been discarded.

The normal infants were born in the thirty-ninth or fortieth week by ordinary forces and suffered no complications in the neonatal period. They were not fed for 12 hours, when they were offered glucose saline; if this was taken satisfactorily the child

TABLE 1
NORMAL CONTROLS

No.	Weight (lb. oz.)	Blood Sugar (mg. %)								
		Cord Blood	Hours after Birth							
			½	1	2	3	4	6	8	12	24
1	7 11½	110	95	102	133						99
2	4 1	69			75		94	77		125	90
3	5 15	83		91	49		68	45		47	
4	8 0	86	77	81	77			62		59	
5	5 10			75				118		81	
6	8 0	53		58	65			65			
7	5 5	85			24		26	36			28
8	5 5	77					32	30			30
9	7 5	109						98			
10	6 15	116		125						116	120
11	7 14	111		104	82		98	77			
12	7 11	75		94	65		77	70			
13	7 7	123	78	69	60		52	55			
14		178	95	120			67	100			86
15	7 8	95	168				122				
16	6 4	67								33	90
17	6 0	50								80	
18	5 12	117		125			127			116	80
19	5 12	115					78				
20	7 12	86		95						100	100
21	7 12	76	69		118		60			75	

was put to the breast at 15 hours and routine feeding begun (Table 1). These babies showed a wide scatter of blood sugar levels at any one interval of time (Fig. 1), but the bulk of the results lay around the mean (Fig. 1). The graph does not show any sudden rise or fall of blood sugar and it suggests that the majority of newborn infants soon attain a reasonably stable blood sugar level. The infants concerned had normal births with uncomplicated neonatal periods: in spite of the fact that four of the results were below 30 mg. % no symptoms suggesting hypoglycaemia were observed.

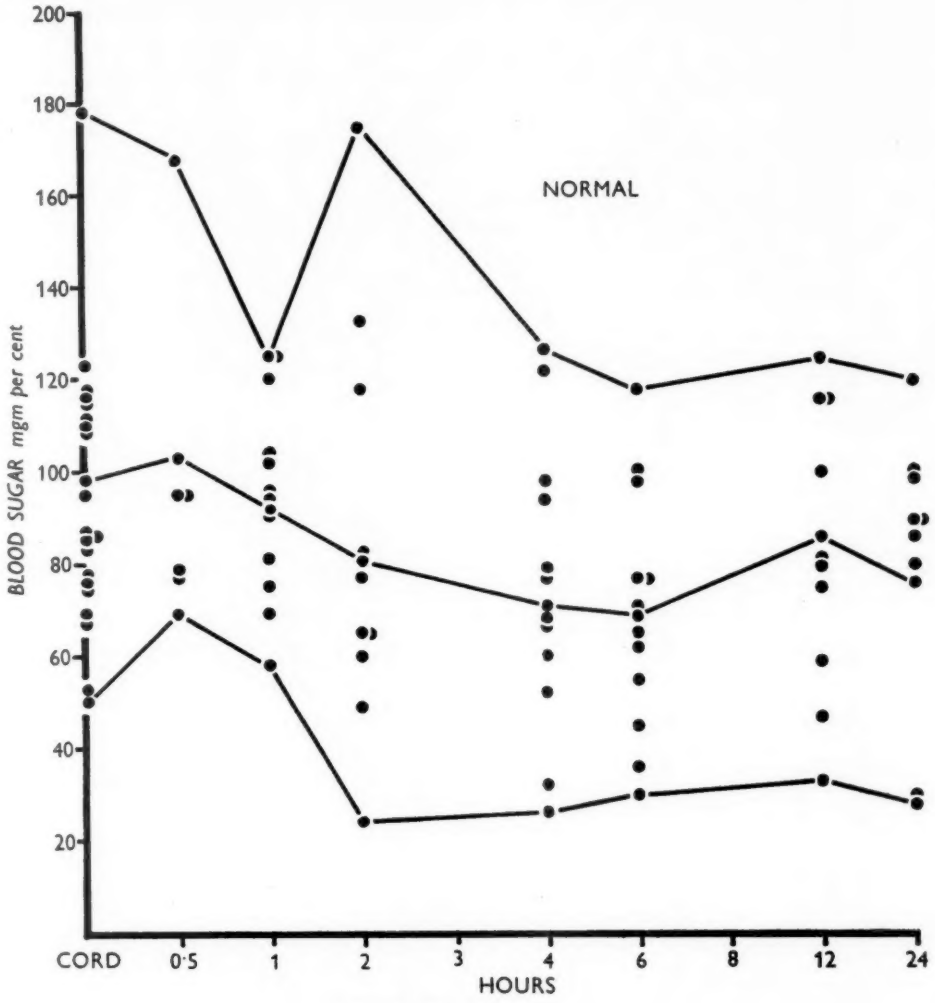

FIG. 1.—Normal controls.

The results obtained in the babies born of diabetic mothers showed considerable variation with a marked drop in blood sugar level during the first two or three hours of life. Once this drop occurred the infant usually stabilized slowly at a rather lower level than that of the normal infant (Figs. 2 and 3).

A comparison has been made between the infants given glucose (25 in all) during the first eight hours (D + g) and those (15 in all) who were left undisturbed (D − g). It can be seen that there is no significant difference between the average figures plotted (Fig.4), although the figures in the D + g group are slightly higher. It is felt, therefore, that there is no indication for the routine administration of oral glucose solutions to the infants born of diabetic mothers. One is lead to this decision by the figures recorded and by the knowledge that these children behave as premature babies and must be treated as such: many of them require oxygen during the first hours of life because of respiratory distress; in

addition drowsiness and a poor cough reflex are often found and one is of the opinion that the early routine administration of fluid solutions with the resulting disturbance of the child might give rise to in these babies and to determine whether this state contributes to the high mortality rate.

Several workers have commented upon the remarkable absence of any unusual symptoms in

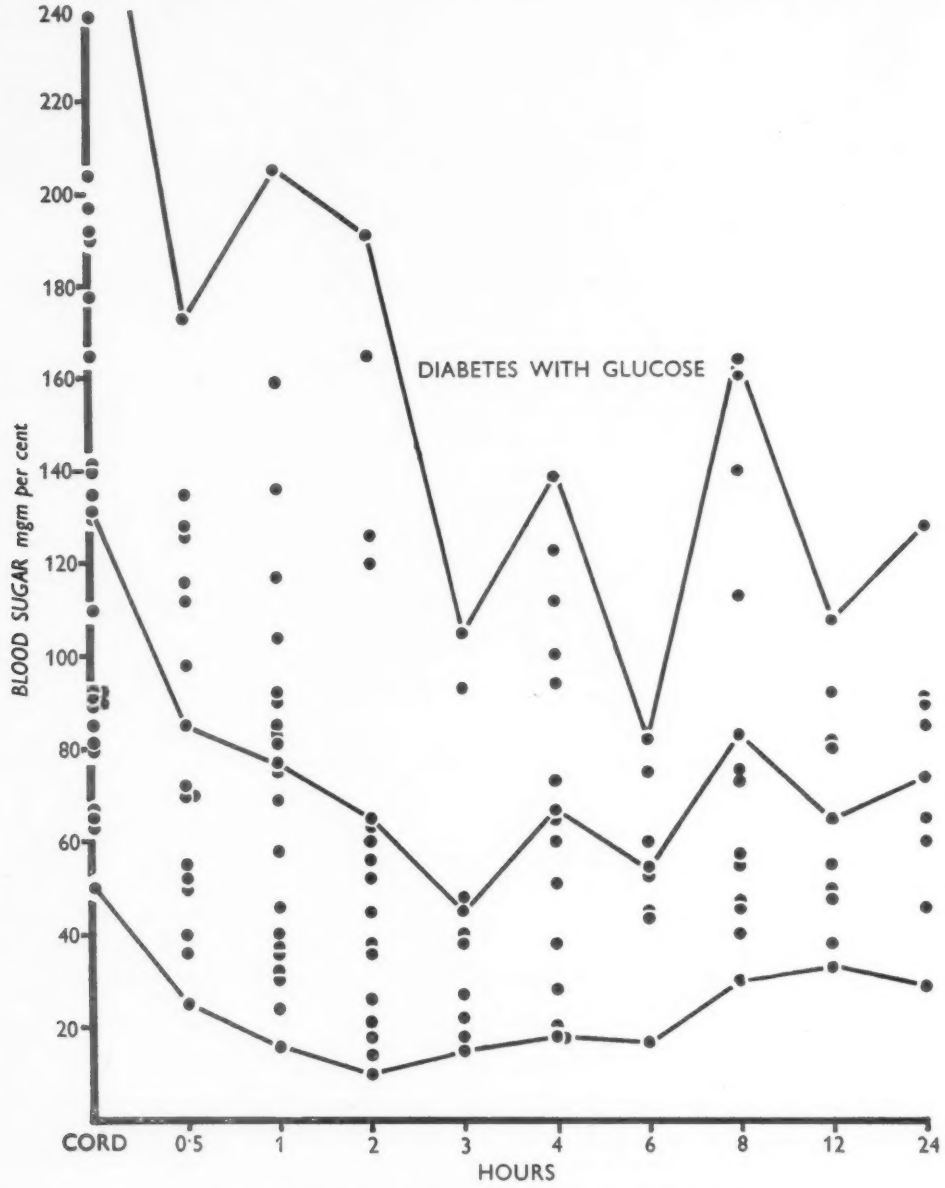

FIG. 2.—Babies born of diabetic mothers given glucose (D+g.)

more harm than good. It has, therefore, been decided to reserve the oral glucose solution for those babies presenting the clinical signs of hypoglycaemia.

The final and main purpose of this study is an attempt to assess what constitutes hypoglycaemia premature or new-born babies presenting with very low blood sugar levels (Joslin *et al.*, 1952; Norval *et al.*, 1950; Oakley, 1953; Pedersen, 1952; Sheumack, 1949; Smith, 1951). In a recent paper Oakley (1953) estimated the blood sugar levels at two-hourly intervals in a series of 35 children, of whom 17

received 50% glucose. He does not give his results in detail but says that very low levels were estimated in children who survived satisfactorily: in three infants who died the blood sugar levels dropped to 35 mg., or less, per 100 ml. Pedersen (1952) in a comprehensive study of blood glucose levels in the infants born of diabetic mothers, says that clinical symptoms of hypoglycaemia were not observed in the first 24 hours of life, and suggests that the onset of any severe symptoms (cyanosis, twitching, grunting respirations) demands a thorough examination of the child in order to exclude complications such as atelectasis, cerebral haemorrhage, infection and heart disease.

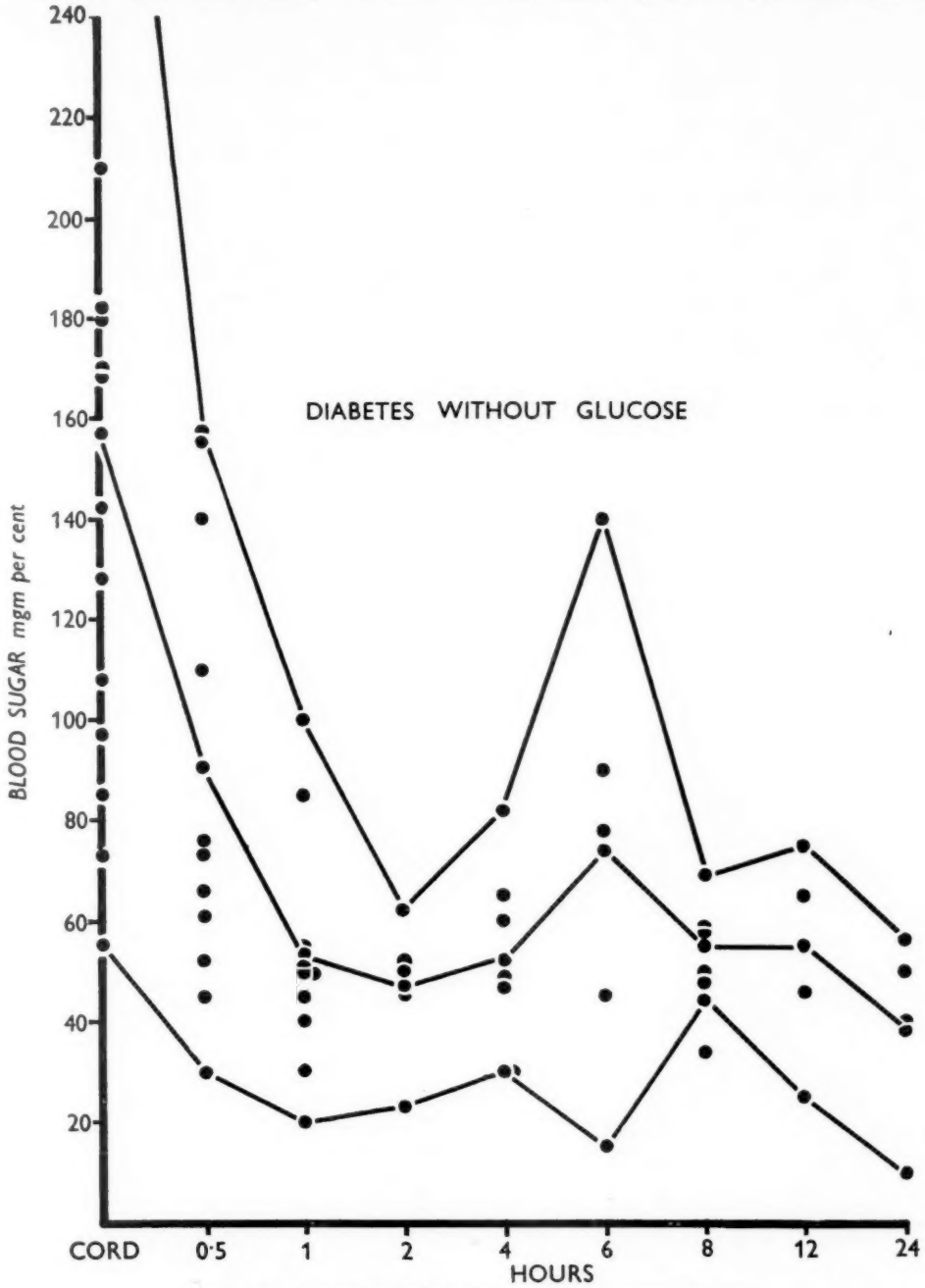

FIG. 3.—Babies born of diabetic mothers not given glucose (D–g.)

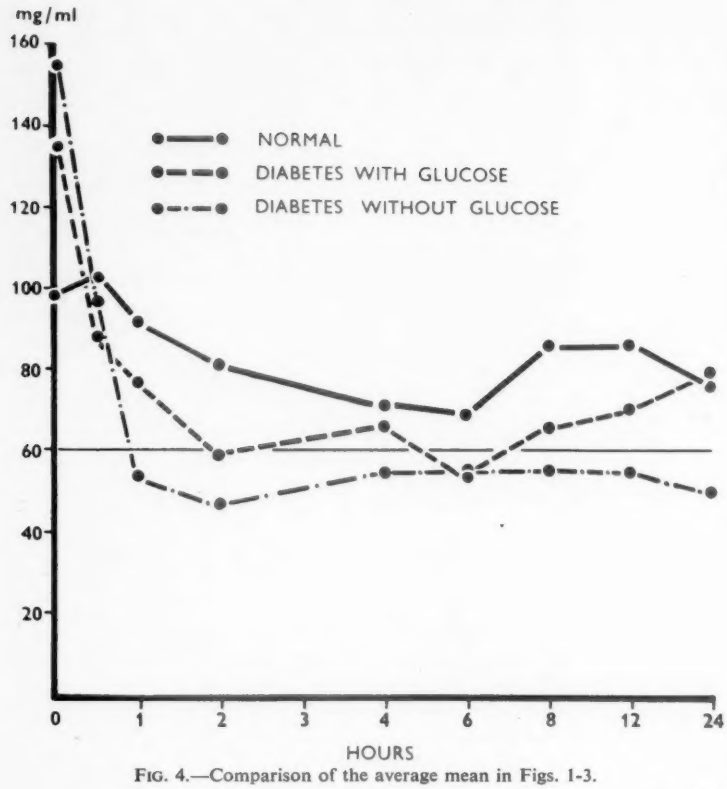

FIG. 4.—Comparison of the average mean in Figs. 1-3.

It can be seen (Tables 2 and 3) that the blood sugar levels in our cases frequently fell below 40 mg. %, a level which Hartmann and Jaudon (1937) suggested was (Tables 2 and 3) indicative of moderate hypoglycaemia, and many were below 35 mg. %. In spite of the most careful clinical observations we saw only four children in whom the symptoms suggested hypoglycaemia; in these infants pallor, a sudden drop in temperature, shallow respirations and occasional twitching were noted. The recorded blood sugars in three cases were as follows: 14 mg., 18 mg. and 18 mg. % respectively; the other infant experienced a rapid drop of 226 mg. % in one hour. There were, in contrast, infants with levels of 10 mg., 15 mg. and 20 mg. % who were symptom free.

It is our belief that, in spite of the low blood sugar levels recorded in the first hours of life of the babies of diabetic mothers, the clinical picture of hypoglycaemia is very rare as all infants are more capable of accommodating themselves to sudden reductions and low levels of blood sugar than are their elders.

In this series of 'diabetic' babies there have been seven deaths and Table 4 describes the pathological diagnoses and the recorded blood sugar levels. In each case there was an obvious cause of death, intracranial haemorrhage being the commonest factor. The infant Sefton did have a rapid fall of blood sugar in the first hour, but as his cord haemoglobin was 75% and his condition desperate from birth, it is our opinion that the subcapsular

TABLE 2
BABIES BORN OF DIABETIC MOTHERS GIVEN GLUCOSE

No.	Weight (lb. oz.)	Blood Sugar (mg. %)									
		Cord Blood	Hours after Birth								
			½	1	2	3	4	6	8	12	24
1	4 13	178	173	83	54		112		161	82	85
2	6 4½	300		159	126		60		73		91
3	7 3	81		37							
4	7 10	241	128				73		40	48	128
5	7 2	50	70	46	36					55	
6	2 5	192	135								M
7	5 11	190	112	73				82		108	
8	6 8	197		205	120						
9	6 3	67			165		65				
10	6 14	85		82	45		51				
11	7 12	92	98	117	60		139				
12	6 12	91		40	38			60			
13	4 4½	140	116	90	56	48	100		164	M	
14	8 4	141	70	32	26	22	18 H			38	
15	10 5	130	52	36	10 N	27	38	45	57	80	
16	6 15	110		92	18	15 H	28	53	75	92	
17	7 2	90	25	16	14 H	18	18	17			
18	5 15	90	72	69	64	93	94	75		50	
19	7 11	92	40	30		38			47		60
20	7 10	80	55	58		40		44	46		46
21	4 5	135		85		105			55		65
22	6 4	204		104							
23	6 4½	65	126	136	191		123		113		90
24	7 0	165	50								
25	6 12½	63	36	24	21		20 N		30	33	29

M = death; H = hypoglocaemia; N = no symptoms.

TABLE 3
BABIES BORN OF DIABETIC MOTHERS NOT GIVEN GLUCOSE

No.	Weight (lb. oz.)	Blood Sugar (mg. %)									
		Cord blood	Hours after Birth								
			½	1	2	3	4	6	8	12	24
1	6 9	55		85	50		65		59		
2	6 0	85		51	48		49		69		
3	5 8¾	142									
4	8 2	97	73	54	23		47				40
5	9 6	210		50	46			78		75	
6	5 7		140	30					M		
7	12 6	180	110	100	52		60	140	48		
8	3 11	73	52	50				M			
9	8 2	182	157	45	66		82	90	50	25	
10	7 6		45	20 N			30	45	44		50
11	8 12	290	76 H							65	56
12	8 8	169	156	55					58		M
13	6 12½	128	66								
14	7 7	170	30	40				30	15 N		10
15	4 10½	108	61						34	46	

M = death; H = hypoglocaemia; N = no symptoms.

TABLE 4
DETAILS OF NEONATAL DEATHS

Initials	Maturity	Blood Sugar Levels (mg. %) 0	½	1	2	4	8	12	Lived	Anatomical Diagnosis	Weight (lb. oz.)
C.G. ..	36 weeks	140	116	90	56	48	100	164	13 hours	Hyaline membrane Haematoma liver Follicular ovarian cysts	4 4
Sefton ..	35 ,,	140	–30						10 ,,	Subcapsular haematoma liver Prematurity	5 7
S.W. ..	33 ,,	73	52	50	15	20			6½ ,,	Intra- and peri-ventricular haemorrhage Hyaline membrane Atelectasis Prematurity	3 11
Stephen ..	36 ,,	169	156	55			58		20 ,,	Hyaline membrane Atelectasis lung	8 8
M.D. ..	31 ,,	No sugars done (too ill)							15 ,,	Intraventricular and subarachnoid haemorrhage Subcapsular haematoma liver Asphyxia	4 7
W.H. ..	32 ,,	No sugars done (too ill)							3 ,,	Intraventricular cerebral haemorrhage Prematurity	5 9
D.B. ..	36 ,,	192	135						5 days	Tiny baby (twin) Meningo-myelocoele	2 5

bleeding occurred before birth, and that the subsequent lowering of the blood sugar was not a major contributory factor to death. (In this case respiration was never properly established and gentle rocking was employed together with oxygen therapy for several hours.)

The low figure in the case S.W. was associated with symptoms suggesting hypoglycaemia, but in view of the necropsy findings it is unlikely that death was hastened by the hypoglycaemia. There is no evidence that this condition contributed to death in any of the other cases recorded here.

Summary

Estimations of the blood sugar level during the first 24 hours of life were made on 21 normal infants and 40 infants born of diabetic mothers. Twenty-five of the latter 40 babies were given 50% glucose in the first eight hours of life.

The normal infants showed a wide scatter of blood sugar levels but there was no dramatic rise or fall in the figures in any one case.

The babies of diabetic mothers revealed a rapid drop in the first hours of life with a slow rise towards the end of the first 24 hours. There were considerable variations in the figures obtained.

The administration of a 50% oral glucose solution did not make any appreciable difference to the blood sugar levels obtained compared with the group of infants to whom glucose was denied.

The clinical picture of hypoglycaemia in infancy is described and the fact that it is an uncommon finding is stressed.

It is suggested that few, if any, babies born of diabetic mothers die as the result of hypoglycaemia.

I am grateful to Professor W. I. C. Morris and Professor W. F. Gaisford for the opportunity to carry out this work. I am much indebted to Mr. H. Varley and the staff of the biochemical department for their assistance and to the various paediatric residents who have assisted in the general supervision of these cases. Finally, my thanks are due to the Department of Medical Illustration at the United Manchester Hospitals for their help with the graphs.

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LABORATORY OBSERVATIONS ON THE VISCIDITY OF MECONIUM

BY

JOHN L. EMERY

From the Department of Pathology, Children's Hospital, Sheffield

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Abnormalities in intestinal function associated with changes in meconium, which are usually discussed under the heading of meconium ileus, are responsible for many deaths in the newborn period. Disorders produced by meconium would seem to be largely due to intestinal obstruction due to the meconium being unusually tenacious and firm. The basic constituents of normal meconium have been known for 50 years (Zweifel, 1875; Lewin, 1900) and have recently been the subject of study by Rapoport and Buchanan (1950). We know, however, little of changes in composition of meconium related to the variation in its physical properties. Until more is known our treatment of diseases associated with abnormal meconium is likely to be arbitrary and unsatisfactory.

The present study was undertaken in an attempt to determine some factors related to the tenacity of meconium. The features studied were 'surface tension', water content, tryptic activity and the nitrogen content of dried meconium.

Materials and Methods

The meconium came from a series of necropsies on infants either stillborn or dying a few hours after birth. A further few abnormal specimens were obtained from children dying up to five days after birth from diseases of the intestine.

The consistency of the meconium varied so much that the only satisfactory method of assessing its physical nature appeared to be that of measuring the 'tackiness' of its surface. This was determined by finding the weight necessary to pull a small metal ring, of internal diameter 11·8 mm., made of 0·14 mm. nickle wire, away from the surface of the meconium in a small dish. The principle involved is that of the standard method for the estimation of surface tension by the use of a torsion balance. Since 'surface tension' is a measure of the tendency to contract of the free surface of a liquid and meconium does not appear to be a Newtonian fluid with a free surface, the method used here is not a measure of what is usually termed surface tension. It is rather a measure of the combined adhesiveness and strength of the meconium, i.e. more related to what is termed plasticity or viscosity in a Newtonian fluid. The apparatus used gave a constant reading of 0·56 g. for the surface tension of water. The numbers obtained as weights are of necessity arbitrary and simply of relative value. The method, however, appeared to give remarkably constant readings. Such readings rarely showed a variation of more than 0·02 g.

The water content was obtained by drying a known weight of meconium on a hot plate at 95° to a constant weight.

The tryptic activity was measured using the simplification of the method of Andersen and Early (1942) previously described (Emery, 1952).

The nitrogen content was estimated on powdered dry meconium using acid digestion and Kjeldahl distillation.

Results

Variation in 'Surface Tensions'.—The adhesiveness of 64 samples of normal meconium was measured. Four further samples of clinically abnormal meconium of meconium ileus type were also examined. The tension of the normal specimens varied from 0·4 to 3·5 g. More than half of the specimens gave readings between 0·5 and 1·5 g., the numerical distribution suggesting a simple logarithmic incidence. The specimens which were clinically abnormal had greatly increased 'surface tensions', the readings being 14·0, 22·0, and 5·8 g., i.e. showing a range of up to 20 times the average normal. No significant difference was seen in the distribution of readings in the meconium samples taken from the ileum and those taken from the colon.

Variation in Water Content.—The water content was estimated in 56 samples of normal meconium and varied from 70 to 92% of the total weight. The majority of samples showed a water content of

between 75 and 85%. These figures are what would be expected to occur in range around the figure of 80% water given by Feldman (1920) and 72·4% by Rapoport and Buchanan (1950). Five specimens reported by Hymanson and Kahn (1919) had a water content of 73·2%, 80·1%, 78·4%, 69·7% and 71·8%.

The water content of three samples of meconium of the meconium ileus type were 62·2%, 63·3% and 55·3%.

Variation in Tryptic Activity.—Tryptic activity was estimated on 48 normal samples and showed a distribution similar to that seen in a previous normal series reported from this laboratory (Emery, 1952).

Variation in Nitrogen Content.—The total nitrogen was estimated in 43 specimens. The levels varied from 4·6 to 15·4 g. % the majority being between 5 and 7 g. No attempt was made to separate the protein and non-protein nitrogen. The nitrogen content of two of the abnormally tenacious specimens of ileus type only were examined and were 6·95 and 6·18 g. %, i.e. close to the mean normal level. The specimens with highest nitrogen levels were in all other respects completely normal.

The figures found were considerably higher than that of 2·33% given by Lewin (1900 quoted by Feldman). Von Reuss (1920) considers the nitrogen content of dry residue to be from 2·1 to 5%, Hymanson and Kahn (1919) give the range of total nitrogen of wet meconium as 0·62% to 1·09% and Trumpp (1912) as 1·45%. The present figures are similar to those (7·1, 5·4, 5·1, 5·8, 6·0 g. %) obtained by Rapoport and Buchanan (1950) but the level of 14·4 g. % suggested as being abnormal by them is within the normal range in the present series.

Relationship between 'Surface Tension' and Water Content.—'Surface tension' and water content were both examined in 56 specimens, and their relationship within the normal range is represented in the target chart in Fig. 1. Of the 27 specimens giving a tension reading of 1 or less, 25 (i.e. 93%) had a water content of 80% or over whereas of the 18 cases having a reading of 1·5 or over, three (16%) only had a similar water content.

The specimens from three cases of ileus type all showed a gross diminution in water content.

Excluding the ileus specimens the correlation coefficient between the 'surface tension' and the water content was, 0·670 ($P < 0·001$) confirming a definite positive relationship of 'surface tension' with dried residue as suggested by the scatter in Fig. 1.

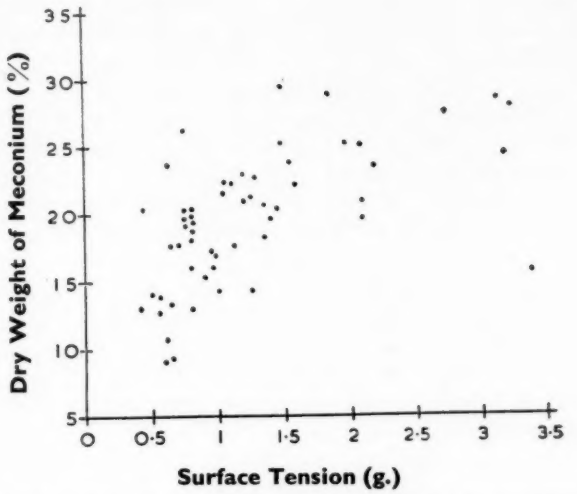

FIG. 1.—The relationship between 'surface tension' and the percentage dry weight of meconium.

Relationship between 'Surface Tension' and Tryptic Activity.—Tension readings and tryptic activity were both estimated on 45 normal specimens. The distribution of their relationship is illustrated in Fig. 2. There appears to be no correlation between the tryptic activity and the surface tension of the specimens of meconium. Of the three specimens of meconium of the meconium ileus type examined, the tryptic activity titre was 1 in 10, 0 and 1 in 40.

Relationship between 'Surface Tension' and Nitrogen Content of Dried Meconium.—Both the adhesiveness and nitrogen content were estimated in 39 normal specimens.

When the specimens were divided on the mean nitrogen content it was found that of 21 specimens

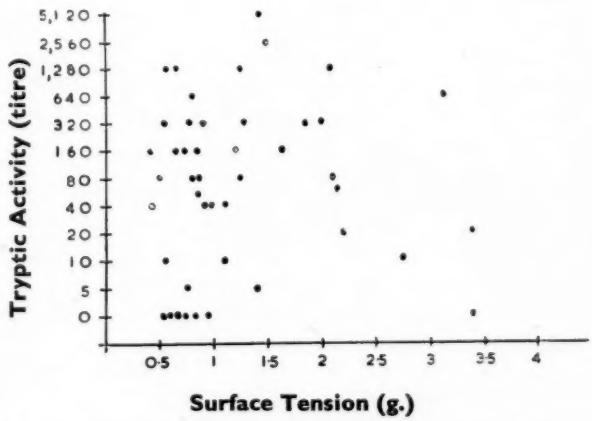

FIG. 2.—The relationship between the 'surface tension' of normal specimens of meconium and the tryptic activity of the specimens.

having a viscosity of 1 or less, 20 had a nitrogen content of over 6·5 g. %. In the specimens with 'surface tension' of 1·5 or over, eight of 11 (72%) had a nitrogen content of below 6·5 g. %.

Examined in another way the correlation coefficient of the 'surface tension' and the logarithm of the nitrogen content gave a value of 0·358, giving a significance of the 0·02 to 0·005 levels. This suggests that there is an inverse relationship between the nitrogen and the tenacity of meconium; i.e. the greater the nitrogen content the more fluid the meconium. It is interesting that the two pathological specimens of meconium with tension readings of 14·5 and 20 had nitrogen levels of 6·18 and 6·95 g. % which are very near the mean level for normal meconium.

Discussion

The most striking observation in this study is the great variation found in all the factors estimated in normal meconium. The question arises whether or not it is legitimate to use meconium obtained at necropsy as being normal meconium. There is, however, little alternative to obtaining meconium in large quantities and uncontaminated by urine than at necropsy or operation. Also children dying within a few hours of birth usually have a cause of death unrelated to the lower alimentary tract, and no difference could be seen between meconium obtained from stillborn children and those dying within a few hours of birth. (It is interesting to note that next to calcified bone meconium is said to be the most durable natural substance of the body (Schmidt, 1897).)

The observation that the tenacity of the meconium bears a direct relationship to the water content of the meconium is not surprising. Gross (1953) in discussing meconium ileus refers to the degree of 'dryness' of the abnormal meconium on purely clinical grounds. From what we know of meconium at the present time it would seem that it consists principally of long-chained molecules of the muco-polysaccharide and muco-protein group. It would seem probable that meconium is not a simple liquid with the muco-protein in solution but a series of 'dispersed systems' (Reiner, 1949) and that the tackiness or viscidity of meconium is determined by the amount of water lying between large molecular masses. In view of the known high rate of fluid transference within the post-natal alimentary tract, it is possible that a minor disturbance in the onset of normal fluid exchange could account for a pathological state of meconium within the bowel.

The value of the negative correlation found between nitrogen content of the dried meconium and its viscidity is difficult to interpret due to our lack of knowledge of the nitrogen linkage within the meconium. But in view of the findings of Rapoport and Buchanan (1950) that a major constituent of meconium is a muco-polysaccharide it seems possible that there is an inverse relation between the quantity of muco-polysaccharide and muco-protein in meconium. Thus the inverse relationship between the nitrogen content and the viscidity may indicate a positive relationship between the viscosity and muco-protein. Rapoport and Buchanan suggested that the enhanced viscosity of meconium in meconium ileus was due to muco-protein being more viscid than muco-polysaccharide and the disease due to an absence of ferments digesting the muco-protein. The finding in the present study of no correlation between viscidity and the tryptic activity of meconium is difficult to associate with the above hypothesis. It is, of course, not possible to relate the tryptic activity of meconium to the total functional activity of the pancreas, but in all the cases from which meconium was used the pancreas was examined histologically and no changes suggesting fibrocystic disease were found. It seems likely that the tenacity of the meconium within the normal range is not directly related to tryptic secretion of the pancreas. In meconium ileus pancreatic changes are always found by some authors (Bodian, 1952) but cases of meconium ileus having apparently normal pancreatic function have been described (Hinden, 1950). Farber (1944) suggested that different factors might be effective in different cases of meconium ileus. It is quite possible that the pancreatic changes seen so frequently in meconium ileus may not be the primary site of disease.

The specimens of meconium causing obstruction in the present series showed a grossly diminished water content, a normal nitrogen content and a normal or low tryptic activity. The present study suggests that the water content in meconium is a potent factor in determining its viscosity.

Summary

A series of 64 specimens of normal meconium were examined for 'surface tension', water content, nitrogen and tryptic activity. Extremely wide ranges were found in all factors. The viscidity of the meconium is directly related to the water content. It appears to be inversely related to the nitrogen content, and unrelated to the tryptic activity of meconium. Specimens from four cases of meconium obstruction showed a greatly diminished water content, normal nitrogen and normal or low tryptic activity.

It is a pleasure to acknowledge the help of Miss C. Roseman, Statistician to the University of Sheffield. for the help in statistical analysis, and to Mr. H. R, Norman, B.Sc., who carried out the nitrogen estimations.

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HAEMOGLOBIN LEVELS IN PREMATURE INFANTS

BY

MALCOLM ARTHURTON, DONOUGH O'BRIEN and TREVOR MANN
From the Institutes of Obstetrics and Child Health, Hammersmith Hospital, London

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Most existing accounts of haemoglobin values in healthy premature infants covering the early weeks of life were written before many of the errors of such determinations were recognized. Because of these limitations it was decided to review the normal values for the first three months of life. The results were compared with a small series of readings made on a group of healthy, full-term infants.

Method of Investigation

Two hundred blood samples were taken, 185 of these being from a scalp vein, 13 from other veins (external jugular, antecubital or femoral), and in two instances heel-prick specimens were used. About 0·5 ml. of blood was withdrawn into a well-fitting sterile 2 ml. all-glass syringe and placed at once in a tube containing a small quantity of dry heparin. After mixing 20 c.mm. of blood was pipetted into 4 ml. of 0·04% ammonia solution. The haemoglobin percentage was then read off directly in an 'M.R.C. grey wedge photometer'. In this instrument a scale reading of 100% is equivalent to 14·8 g. Hb/100 ml.

All samples were taken and all readings made by the authors and the average of six readings was taken as the final result. The photometer itself was checked at frequent intervals against a grey screen of known density and on three occasions blood samples of known haemoglobin concentration supplied by the M.R.C. Haemoglobin Standards Scheme were tested. Readings made by each of us on these occasions did not vary by more than 0·5 g. Hb/100 ml. from the expected figure.

During the first part of the study serial haemoglobin estimations were made on 22 healthy premature infants whose birth weights ranged between 2 lb. 7 oz. and 5 lb. 3 oz. Table 1 shows the distribution of cases in four groups according to birth weight.

TABLE 1
PREMATURE INFANTS

Birth Weight Range (lb./oz.)	1·9–2·8	2·9–3·8	3·9–4·8	4·9–5·8
No. of Infants ..	1	8	10	3

Six infants were born at home and subsequently admitted to the Premature Baby Unit. Six were the survivors of multiple births. An average of six estimations was made on each infant during the first three months of life, the initial reading being made as soon as the baby's clinical condition was satisfactory.

In the second part of the study a few haemoglobin determinations were made by the same technique on each of 17 healthy full-term infants for comparison with the first series. Table 2 gives the distribution of the cases between four birth-weight groups.

TABLE 2
FULL-TERM INFANTS

Birth weight range (lb./oz.)	5·9–6·8	6·9–7·8	7·9–8·8	8·9–9·8
No. of Infants ..	3	6	6	2

Two readings were obtained in the Maternity Unit during the first 10 days of life and two further ones were made in the infant follow-up clinic between the fortieth and sixtieth and the eightieth and hundredth days. In two cases a final reading was not obtained.

None of the babies in either group was given iron therapy or a blood transfusion during the period of the investigation. The normal practice in the premature baby unit is to give iron at the age of 6 weeks or on discharge from hospital if this occurs sooner. Breast milk is largely used for feeding in hospital. When artificial feeding becomes necessary Half Cream National Dried Milk, which does not contain added iron, is given. The possibility that some of the babies in the two groups were fed on an iron-fortified proprietary dried milk on returning home cannot be excluded.

Results

Premature Infants.—Fig. 1 shows the individual readings and the day of life on which they were

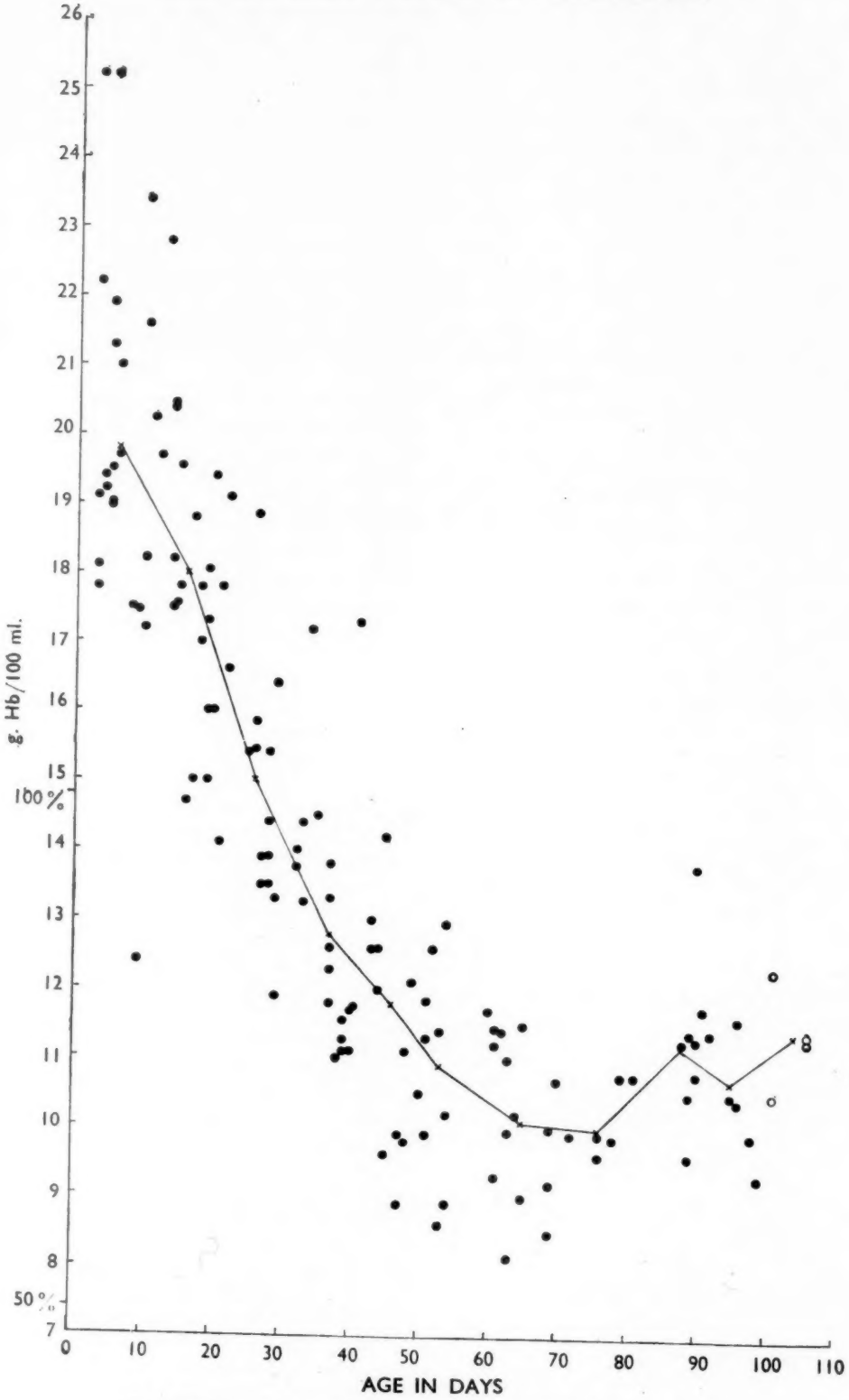

FIG. 1.—Premature infants: individual readings with graph of average values.

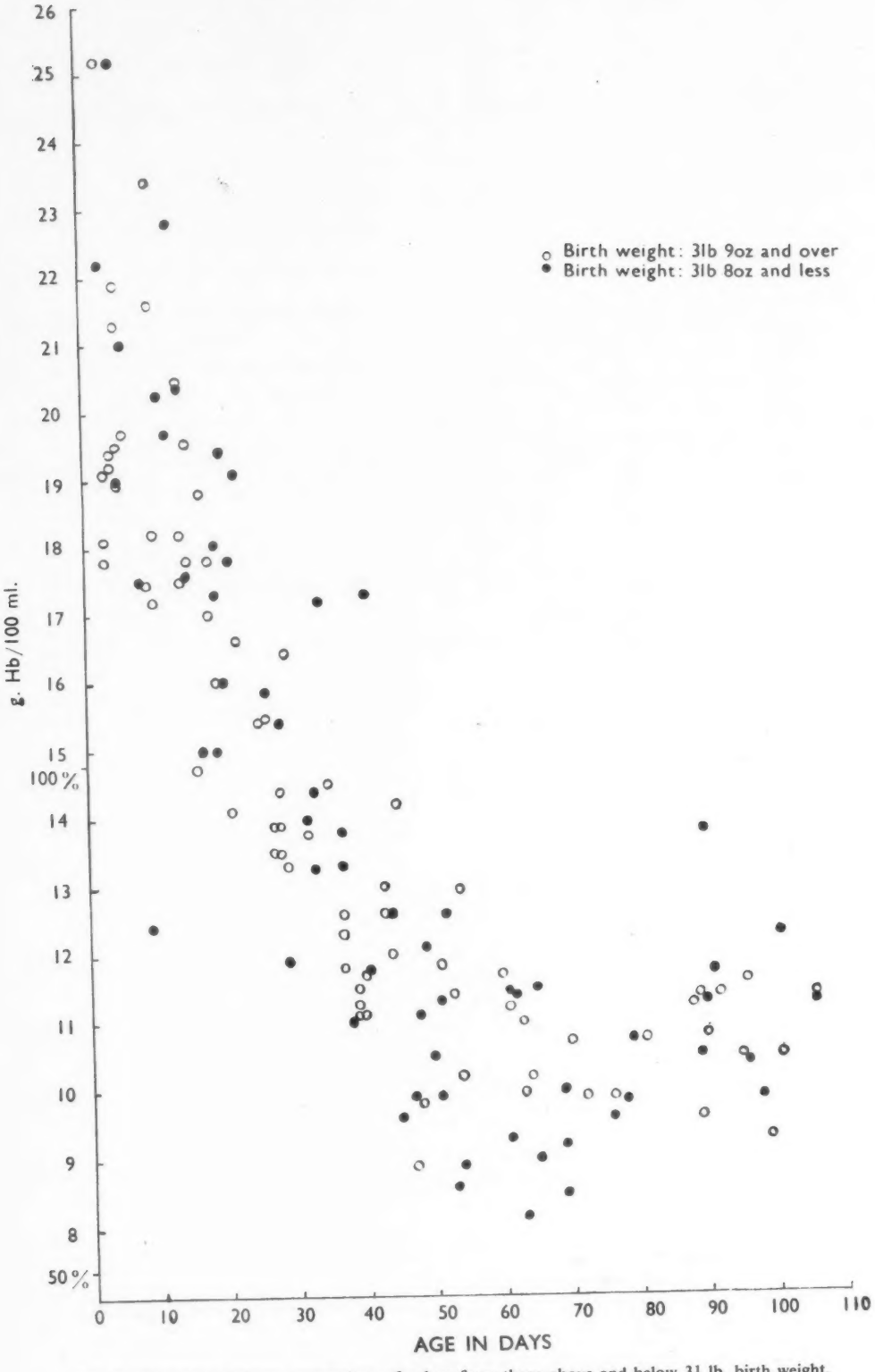

FIG. 2.—Premature infants: comparison of values from those above and below 3½ lb. birth weight.

obtained.* The highest initial level was 25·2 g. Hb/100 ml. recorded on the third and fifth days respectively in two babies. The lowest initial reading was 12·4 g. Hb/100 ml. found on the ninth day. The lowest value recorded during the investigation was 8·2 g. Hb/100 ml. on the sixty-third day. A consideration of the individual haemoglobin trends showed that there was a tendency for the levels of babies with initial readings above 20 g. Hb/100 ml. to fall more than 10 g. Hb/100 ml. and those starting below 20 g. Hb/100 ml. to fall less. In two cases it was noted that the haemoglobin concentration rose between the initial readings on the third and fifth days respectively and the second observations on the fourteenth day.

Fig. 1 also shows the averages of all readings made in each 10-day period plotted at points representing the average time at which they were obtained. The curve shows the decline of average haemoglobin values to be maximal between the second and fifth weeks. The fall ceases between the ninth and eleventh weeks and thereafter there is a rise to 11·4 g. Hb/100 ml. by the fifteenth week. The small rise on the curve just beyond the trough is probably due to the fact that the last four points on the graph are based on small numbers of cases. Although the curve of average values reaches its lowest level of 10·1 g. Hb/100 ml. on the seventy-sixth day, there was considerable variation of the time at which individual children reached their lowest reading. Thus in some cases the lowest point of the curve was reached on or before the sixtieth day whereas in others the levels were still falling at that time.

Fig. 2 shows the scatter of readings of premature infants divided into two groups according to whether or not their birth weights exceeded 3½ lb. The figures for the two groups are well admixed, but of the six values of 9·0 g. Hb/100 ml. or less, five were obtained from infants in the lower weight group.

In Fig. 3 the curve of average values in Fig. 1 is compared with average readings obtained in premature infants at different ages by Merritt and Davidson (1934) and by Mackay (1935). It will be seen that our figures correspond very closely with theirs.

Full-Term Infants.—The highest initial level was 22·9 g. Hb/100 ml. on the fourth day. In four babies the haemoglobin concentration rose between the initial readings made on the third or fourth day and those on the ninth or tenth day. The average readings for the full-term series are shown in Table 3 as the infrequency of observations does not permit the construction of a graph of any value. Table 3 also shows the average day on which these readings were made and the number of readings upon which the average haemoglobin values are based. The fact that the average level appears to be still falling at the ninety-first day is almost certainly misleading and is probably accounted for by the trough of the curve lying somewhere between the third and fourth readings (i.e. between the forty-seventh and ninety-first days).

TABLE 3
FULL-TERM INFANTS

Age (in days)	0–5	6–10	42–52	83–99
Average value (g.Hb/100 ml.)	19·1	18·4	13·3	12·6
Average day of readings	3·3	9·4	47	91
No. of readings ..	17	16	17	15

In Table 4 average haemoglobin values for premature and full-term infants are compared at four periods during the first four months of life for which there are an adequate number of readings in each group. During the first two weeks of life the two average values found for the premature group exceed the two corresponding ones for the full-term series by approximately 1·0 g. Hb/100 ml., but the difference is not statistically significant. After the sixth week, however, the position is reversed, the two average levels for the full-term babies being between 1·0 and 2·0 g. Hb/100 ml. higher than the two corresponding levels for the premature ones—a difference that is now significant.

TABLE 4
VALUES FOR PREMATURES AND FULL-TERM INFANTS COMPARED

Time Period (inclusive days)	Prem.	F.T.	Prem.	F.T.	Prem.	F.T.	Prem.	F.T.
	3–5	3–5	6–13	6–13	42–52	42–52	90–100	90–100
Average day of readings ..	4	3·4	9·5	9·4	47	47	94	94
No. of readings in each period ..	13	16	12	16	16	17	10	9
Average value (g. Hb/100 ml.) ..	20·4	19·1	19·3	18·4	11·4	13·3	11·1	12·6

Discussion

In recent years there has been an increasing awareness of the instrumental, technical and subjective

*Full results have been deposited with the British Museum (Natural History) Cromwell Road, London, S.W.7, and can be obtained by anyone interested.

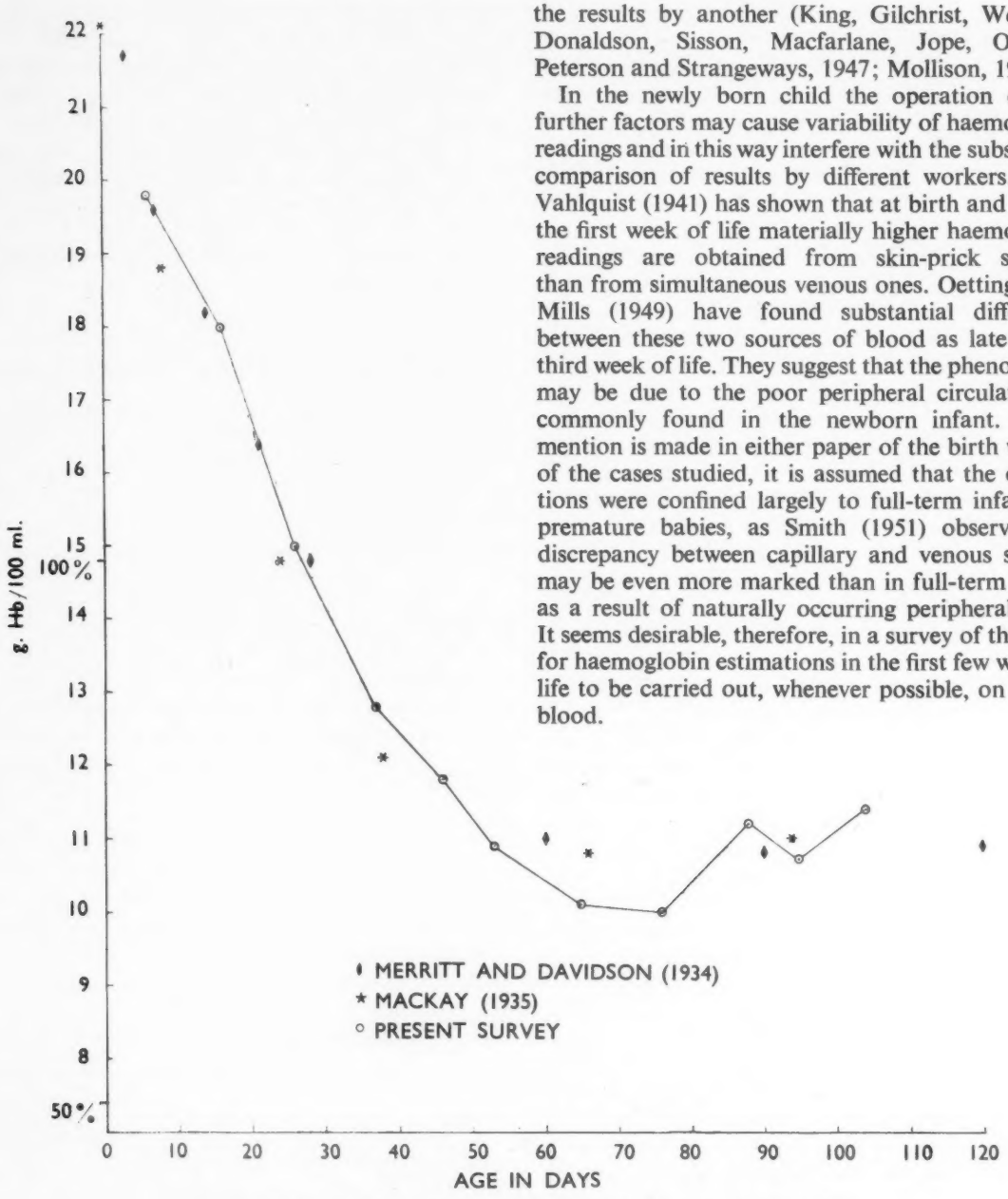

FIG. 3.—Premature infants: average values compared with those of other authors.

factors which may affect the accuracy of haemoglobin estimations. Macfarlane (1945), for instance, enumerates a number of sources of error which may lead to wide differences in the estimates by two or more observers on a divided sample of blood. The importance of accurate haemoglobin standardization has not been generally appreciated in the past and accordingly the results obtained by one method have not always been capable of comparison with the results by another (King, Gilchrist, Wootton, Donaldson, Sisson, Macfarlane, Jope, O'Brien, Peterson and Strangeways, 1947; Mollison, 1951).

In the newly born child the operation of two further factors may cause variability of haemoglobin readings and in this way interfere with the subsequent comparison of results by different workers. First, Vahlquist (1941) has shown that at birth and during the first week of life materially higher haemoglobin readings are obtained from skin-prick samples than from simultaneous venous ones. Oettinger and Mills (1949) have found substantial differences between these two sources of blood as late as the third week of life. They suggest that the phenomenon may be due to the poor peripheral circulation so commonly found in the newborn infant. As no mention is made in either paper of the birth weights of the cases studied, it is assumed that the obervations were confined largely to full-term infants. In premature babies, as Smith (1951) observes, the discrepancy between capillary and venous samples may be even more marked than in full-term infants as a result of naturally occurring peripheral stasis. It seems desirable, therefore, in a survey of this kind, for haemoglobin estimations in the first few weeks of life to be carried out, whenever possible, on venous blood.

The second factor, and a most important one, is the time when the cord is clamped. It is now well established that the haemoglobin after birth is higher if the cord has been tied late rather than at the moment of birth (DeMarsh, Alt and Windle, 1941), an effect which influences the levels obtained during the first two to three months of life (Johnson, 1948). DeMarsh, Windle and Alt (1942) estimate that the newborn child at term may be deprived of about

100 ml. of blood if the cord is tied promptly after birth. Such deprivation is probably of greater significance to premature infants, since Barcroft (1946), working with sheep, has shown that the ratio of placental to foetal blood volume decreases as pregnancy advances.

In this survey we have tried to reduce known and avoidable errors. The use of the M.R.C. photometer, as described, has enabled us to express our results in terms of a colour standard established by the National Physical Laboratory, and to eliminate some of the sources of error in colour matching referred to by Macfarlane (1945). Venous blood has been used throughout the investigation, except in two full-term babies. To avoid errors resulting from excessive venous congestion (M.R.C. Report, 1945) manual constriction of the scalp was applied only just before sampling. Unfortunately, it has not been possible to control satisfactorily the time of cord ligation in this study. The practice at Hammersmith Hospital of tying it a few minutes and not immediately after birth in both full-term and premature babies probably represents conditions as they occur in most domiciliary and hospital deliveries.

A comparison of our cases after dividing them into two groups according to whether or not their birth weight exceeds 3½ lb. is of some interest. Blackfan and Diamond (1944) have shown in a group of 75 prematurely born infants that the more premature the baby and the less the birth weight the more severe is the physiological anaemia. Comparing our two groups we find that although the smaller infants tend to reach a lower haemoglobin level between the eighth and twelfth weeks of life than the larger ones, the individual readings for the two groups are well admixed in each 10-day period and the difference is not as striking as had been anticipated.

Our findings suggest that blood transfusion has little place in the care of healthy premature infants. Before this survey it had not been considered necessary to transfuse any of 521 normal babies admitted to the Premature Baby Unit. A haemoglobin reading was carried out on each case as a routine just before discharge, unless unusual pallor demanded an earlier estimation. Each child was sent home on an iron mixture and its general condition checked periodically in a special follow-up clinic until the first birthday had been passed.

Iron deficiency anaemia which may appear during the second six months of life did not constitute a problem when this routine was followed. Transfusion would, of course, have been considered in the early months if the haemoglobin concentration had fallen below 8·0 g. Hb/100 ml. or remained at that level for a week or two. Unlike Rossier and Potiron (1952) we do not favour the use of small repeated transfusions as a routine in all premature infants. Although these workers report only six non-fatal reactions in over 1,000 transfusions, we still do not think it justifiable to expose a premature baby unnecessarily to the possible hazards of a procedure which may only serve to inhibit erythropoiesis at a time when marrow activity is on the point of revival and which, furthermore, may increase the possibility of transfusion reactions in later life.

Summary

A study has been made of the trend of haemoglobin concentrations during the first three months of life in 22 healthy premature infants.

All estimations have been made with an M.R.C. photometer on venous samples.

Some possible sources of error are discussed.

The results are compared with readings obtained from 17 healthy full-term infants and with those of some other workers.

Some comments are made on the place of blood transfusion in the treatment of the early anaemia of prematurity.

Our thanks are due to Professor Alan Moncrieff for permission to investigate infants under his care, to Drs. P. L. Mollison and Cedric Carter for their constant help and advice, and to Sister M. Smith who assisted with the blood sampling.

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A CONGENITAL RENAL TUBULAR DEFECT

BY

J. LUDER and DOROTHY BURNETT

From The Hospital for Sick Children, Great Ormond Street, London

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Waring, Kajdi and Tappan (1945) described six cases of severe polyuria and polydipsia which showed no response to pitressin therapy. The onset was after birth and the main features were erratic fever, constipation, vomiting and hyper-electrolytaemia without acidosis. The urine was constantly of low specific gravity, and in spite of high fluid intakes it was difficult to maintain hydration. Pitressin had no good effect in doses up to a toxic level.

A similar condition in seven members of one family was reported by Williams (1946). In at least two the condition began in infancy, with one death. Moderately impaired kidney function was found in five adult cases, but not severely enough to cause marked ill-health.

Dancis, Birmingham and Leslie (1948), in presenting a further case in a child of 6½ months, demonstrated that the pyrexia coincided with periods of dehydration, that diuresis of a low specific gravity urine persisted in spite of complete withdrawal of fluids, and that the patient's urine contained a normal amount of anti-diuretic substance. They inferred from this that the kidney did not respond to anti-diuretic hormone.

We report here a further case of this rare condition in which there was associated retardation of growth and mental development.

Case Report

Paul A. was admitted at the age of 9 months with a history of occasional vomiting from 4 months, failure to thrive since 6 months and diarrhoea for one week.

He was born of young Jewish parents after a full-term normal delivery with a birth weight of 7 lb. 7 oz. and was breast fed for two months. Artificial feeding with a half-cream milk was continued for a further two months, when mixed feeding was begun. At this time he had a febrile illness of unknown aetiology lasting a few days and his symptoms began after this. He reached a weight of 14 lb. 1 oz. at 6 months and this had fallen to 13 lb. 9 oz. on admission. His stools had always been hard, and although he took fluids well, he was reluctant with solids. Vomiting had become progressively worse until the time of admission. There were no siblings and nothing relevant was found in the family history.

On examination he was a hypotonic, moderately wasted and dehydrated baby of normal colour. He was alert and played with toys, but could not lift up his head or sit up. No teeth were present. The temperature, normal on admission, rose rapidly to 103°F. Slight resistance was offered to neck flexion, and the tonsils were injected, with exudate on the left. No other abnormal physical signs were found.

During his three months in hospital he was consistently dehydrated and had an intermittent pyrexia up to 103°F. Peaks of pyrexia occurred when dehydration was most severe (Fig. 1). Within a few days of admission he was noticed to pass an excessive quantity of urine and to be very thirsty. At this time a raised blood urea was the only biochemical abnormality. An intravenous pyelogram showed no excretion in either kidney. The polyuria and polydipsia persisted throughout, the intake averaging 80-90 oz. daily. The output could not be measured because of incontinence, but two four-hour tests showed a daily average of 50 oz. The specific gravity varied between 1003 and 1007.

One month after admission an episode of convulsions lasting several days ushered in a recurrence of gastro-enteritis, complicated by pneumonia, which responded to intravenous fluids and aureomycin. His condition following this improved, though intermittent pyrexia, polydipsia, polyuria and variable dehydration persisted.

Biochemical Findings.—Normal or high figures were obtained for most of the chemical constituents of the blood.

BLOOD UREA. The blood urea was 68 mg. % on admission and remained persistently around this level, apart from the period during which he was having intravenous glucose solution when it became normal. It later rose to its former level and was above normal on discharge.

SERUM CHLORIDES. The serum chlorides were initially raised (735 mg. %) and showed a progressive fall to normal during the first few weeks.

SERUM SODIUM. The serum sodium was 370 mg. % soon after admission but later fell to the upper limit of normal.

PLASMA BICARBONATE. The plasma bicarbonate level remained at the upper level of normal apart from a period of alkalosis during the gastro-enteritis relapse.

SERUM POTASSIUM AND CALCIUM. The serum potassium and calcium levels were normal throughout.

There was thus a mild degree of hyper-electrolytaemia at the outset, which initially responded to adequate hydration. Before discharge this began to reappear

despite a continued high fluid intake and when seen two weeks later the blood was 87 mg.%, serum sodium 373 mg. %, plasma chlorides 720 mg. %, plasma bicarbonate 52·4 vol. %, serum potassium 18·2 mg. %.

Urea Clearance Test.—Urea clearance tests carried out on three separate occasions showed average maximum clearances of 68%, 76% and 54%.

Pitressin Test. Pitressin tests were performed on two occasions. With the child as hydrated as possible, hourly catheter specimens of urine were measured and specific gravities taken. On the first occasion this was done for one hour only and on the second for three hours in order to eliminate any reflex inhibition of secretion of urine due to catheterization.

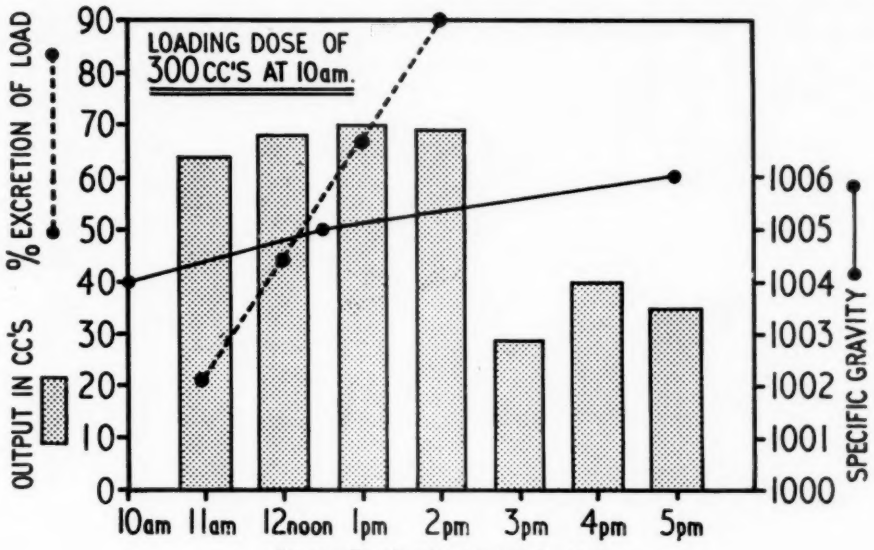

FIG. 2.—Results of water excretion test.

The child was given hourly feeds of his calculated normal requirements during this time. Pitressin was injected intramuscularly in a dose of 0·5 units per square metre of body surface, i.e., 0·15 units, in the first test. The output, specific gravity and chemical composition of the urine were measured for three hourly periods after this. In the second test the dose was increased to 0·75 units. A corresponding test was carried out on a normal child of approximately the same age and weight (Fig. 3).

Water Balance Tests. For 10 hours the child was given hourly quantities of fluid in amounts calculated from his usual intake. At the end of this time he was given a dose of 10 oz. of water; no more fluid was then given for seven and a half hours; then he took 26 oz. during the next hour and was thereafter allowed to drink freely. During the whole of this period the output and specific gravity were measured

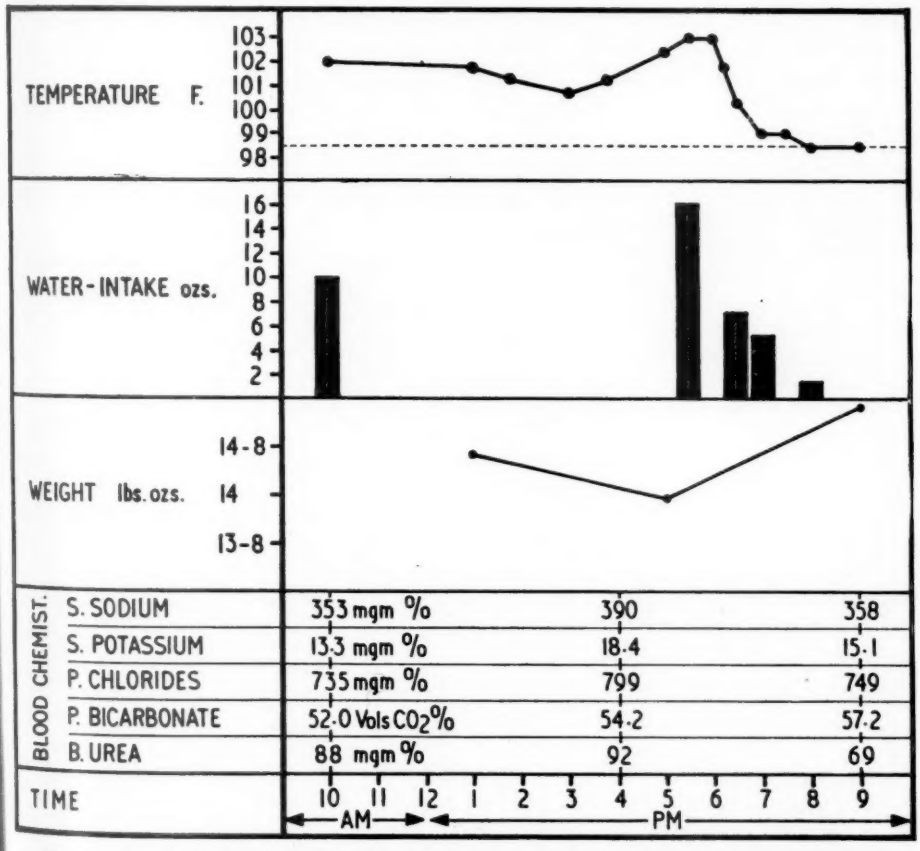

FIG. 1.—Graph showing relationship of dehydration to temperature, weight and blood chemistry.

every 15 minutes, the temperature was taken hourly, and the blood chemistry was checked before, during and after the dehydration period. Fig. 1 shows the changes in temperature, weight, and blood chemistry with dehydration and subsequent hydration, and Fig. 2 shows the urinary output and specific gravity over the whole period.

of the load had been excreted at a constant rate (Fig. 2).

In the ensuing three hours the hourly excretion continued at about half the previous rate, at a time when in normal children almost complete anuria

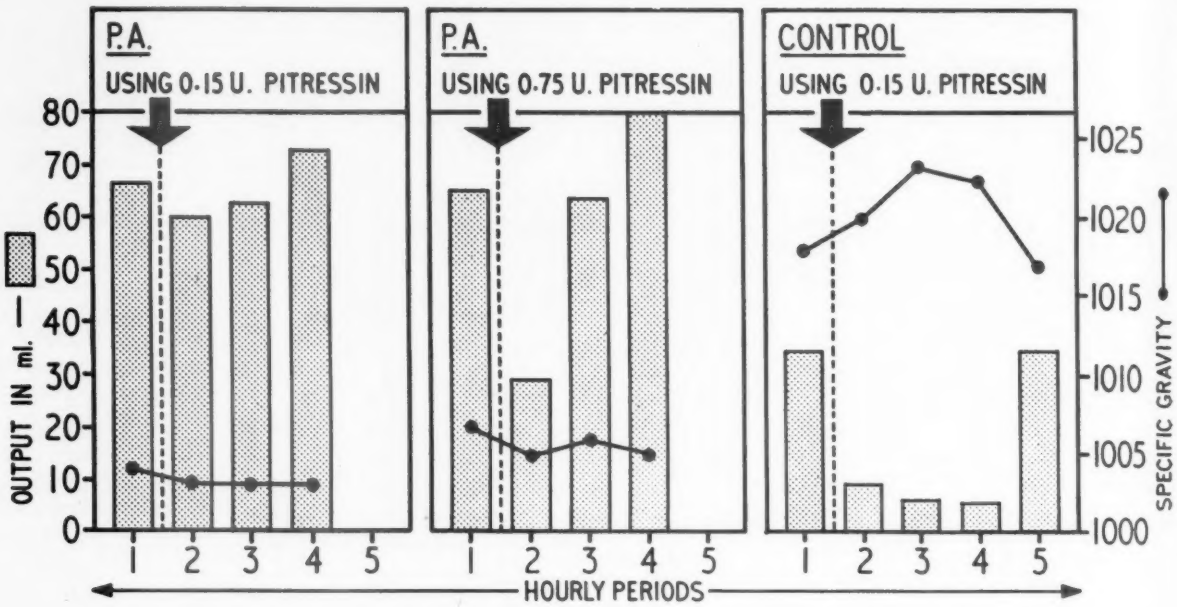

FIG. 3.—Results of pitressin test.

Tests for Anti-Diuretic Hormone (Burn, 1931). Specimens of urine in 2 ml. quantities collected first when the patient was hydrated and later when dehydrated were injected into adult rats, which were at the same time given an adequate water load. Thereafter their urinary outputs were measured every 15 minutes for three hours. Other rats were injected with 5 units and 10 units of pitressin as controls. The hydration specimens caused a delay in diuresis of between 15 and 30 minutes. Dehydration specimens delayed diuresis for 45 to 60 minutes, approximately equal to that obtained with 5 units of pitressin.

Discussion

The case here described is one of a rare group of children referred to at the beginning of this paper who vomit and fail to thrive in the early months of life. Their condition can be distinguished from true diabetes insipidus by their failure to respond to adequate doses of pitressin. Doses higher than 0·75 units were not tried because of reported unpleasant side-effects without anti-diuretic effect (Dancis *et al.*, 1948).

The water excretion test showed a high level of output in the four hours following ingestion of 300 ml. of water. By the end of this time over 90% would have been expected. The specific gravities remained virtually constant throughout, at a low level.

Fig. 1 demonstrates the rapid rise in temperature, fall in weight and haemoconcentration which occurred towards the end of the dehydration period, followed by an equally rapid return to normal when hydrated again. This exemplified his clinical course while in hospital.

Polyuria and polydipsia occur in children with other congenital abnormalities of the kidneys, such as congenital hypoplastic kidneys leading to renal rickets, or congenital cystic kidneys, but in these cases there is always marked impairment of renal function with urea and phosphate retention. Albuminuria and urinary casts are usually present. Our case showed normal values for urea clearance tests, and the blood urea levels, while mainly raised, became normal when the child was fully hydrated. At no time were albumin or casts present in the urine.

Glomerular filtration being therefore within normal limits, the persistent passage of a dilute urine even after dehydration must be due to failure of tubular reabsorption. The presence of anti-diuretic

hormone in the child's urine was confirmed by the rat tests, and the defect must therefore be an inability of the renal tubules to respond. The pitressin tests supported this view. The transient drop in urinary output which occurred in the hour following the injection of 0·75 units is thought to be a vasoconstrictor effect and does not resemble the more prolonged and greater fall in output which occurs in normal subjects, an example of which is shown (Fig. 3*c*).

The management of these cases resolves itself into providing a very high fluid intake sufficient to maintain adequate hydration. In infants this may be as much as 100 oz. daily, and Williams (1946) mentions a figure of 10 pints daily in adult cases.

In our case, the maintenance of such a high fluid intake presented practical problems. The child was reluctant to take solid food after a large volume of fluid, and there was therefore difficulty in maintaining an adequate calorie intake. Conversely, if solids were taken first, the child could not immediately afterwards take an adequate quantity of fluid. However, this was overcome by giving fluids at regular intervals between feeds, including one or more feeds during the night.

We concluded that the best method was to give solid food first, and it was often necessary to give a small dose of sedative beforehand to diminish irritability due to thirst. Fluids were taken after the solid food in small amounts, and a much larger quantity was required within one hour. Calorie intake was increased by giving protein hydrolysate in his fluid feeds.

The prognosis seems very uncertain. Too few cases have as yet been followed up, but of those known to us and those reported in the literature, death has occurred in the early years of life, and others will probably be mentally retarded (Evans, 1953). This condition is not, however, incompatible with normal growth and mental development as has been reported in several adult patients, who apart from requiring a very high fluid intake, were otherwise well (Williams, 1946).

Summary

A case is presented of polyuria and polydipsia resistant to pitressin in a child of 9 months. The main symptoms were vomiting, irritability, failure to thrive and intermittent fever associated with dehydration. The biochemical findings showed a tendency to hyperelectrolytaemia, which could be controlled only with a very large fluid intake. The cause is considered to lie in a congenital defect of the renal tubules in which there is a failure of water reabsorption. Previous cases are mentioned, and suggestions are offered regarding the management and prognosis of these cases.

Our thanks are due to Dr. Schlesinger for permission to publish this case, to Dr. Snaith for performing the antidiuretic hormone assays, to Dr. Payne for his advice on the biochemical findings and to Sisters Thornton and Stott for their excellent cooperation. Mr. E. Cull kindly supplied the diagrams.

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A SECOND CASE IN THE SAME FAMILY OF CONGENITAL FAMILIAL CEREBRAL LIPOIDOSIS RESEMBLING AMAUROTIC FAMILY IDIOCY

BY

N. J. BROWN, BERYL D. CORNER and M. C. H. DODGSON

From the Departments of Pathology and Child Health, Southmead Hospital, Bristol, and the Burden Mental Research Department, Stoke Park Colony, Stapleton, Bristol

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We owe to Norman and Wood (1941) the observation that a disorder resembling amaurotic familial idiocy may originate during the prenatal period and be fully established at birth. Although the importance of this condition was appreciated by Globus (1942), no comparable cases have been reported subsequently. On the other hand, the question of cerebral lipoidosis in early infancy has been fully investigated by Giampalmo (1949) and by Videbaek (1949). In none of the cases reviewed by those two authors, either of the neurological form of Gaucher's disease (30) or of Niemann-Pick disease (73), was the condition undoubtedly present at birth.

A younger sibling of Norman and Wood's original case has recently died in infancy, the main features in the two being almost identical. The condition which these two cases exemplify is thus a familial one whose occurrence appears to be unique in the literature.

Case Report

Margaret C. was born at Southmead Hospital, Bristol, on March 26, 1951. The pregnancy, which had been normal, was of approximately 36 weeks' duration and terminated after a 15-hour labour with a normal vertex delivery. The placenta appeared normal and weighed 1 lb. 6 oz. The infant was only slightly asphyxiated at birth, breathed almost immediately and required no resuscitative measures other than aspiration of some meconium-stained fluid from the pharynx, and no abnormality in her appearance was noted then. The weight at birth was 4 lb. 1 oz., body length 16½ in., head circumference 11½ in., shoulder diameter 4½ in., intertrochanteric diameter 4½ in. During the first four hours of life her condition gave rise to anxiety. Moderate generalized oedema developed, with increased tone in the limbs, amounting to rigidity. There was generalized twitching whenever she was disturbed, and a shrill cry. The anterior fontanelle was small with no increased tension and there was no neck rigidity. In an oxygen tent her colour was normal, although slight cyanosis developed after episodes of twitching.

Her respiration was noted to be abnormal, shallow and very irregular, varying in rate from 44 to 54 respirations a minute, with occasional deep, gasping breaths. The air entry into the lungs was quite good and no adventitious sounds were heard. After 48 hours there was no evidence of oedema, but her condition otherwise was unchanged and as she appeared unable to suck or swallow, feeding by gavage was begun.

During the next 10 days her condition deteriorated. She regurgitated frequently and occasionally vomited larger quantities. Body temperature showed marked thermolability (Fig. 1), which remained an outstanding feature of the case. On the eighth day she suddenly became very much worse with completely irregular respiration, characterized by periods of apnoea of one to two minutes' duration followed by loud, crowing gasps suggestive of laryngeal spasm. The chest showed recession of the lower ribs, diminished basal air entry and some coarse râles. Rigidity was more marked, head retraction developed, and twitching became so severe that feeding was difficult. Lumbar puncture was attempted but no fluid could be obtained. Chloral was administered frequently and also procaine penicillin, as pulmonary infection was feared. Fluid intake was maintained by a subcutaneous drip.

On April 10, when she was 15 days old, her condition was unchanged but it was observed that the general shape of the head was scaphocephalic, with a very poorly developed frontal region and the bi-temporal diameter appeared unusually narrow. Sutures were palpated with difficulty and the anterior fontanelle was almost closed. Throughout the third week her condition remained very poor; she was constantly rigid, in marked opisthotonos, with the limbs held in extension. Her colour became pale and occasionally greyish, but there was never any clinical jaundice. Troublesome abdominal distension was relieved by a flatus tube, regurgitation ceased and oesophageal feeds were well retained, although twitching often made passage of the tube difficult. On the seventeenth day hyperpyrexia with a temperature of 108° F. developed but no signs of infection could be found. Lumbar puncture was again performed and clear, colourless fluid withdrawn under normal pressure.

At the end of four weeks she was clearly still a very

abnormal baby. Her weight was 4 lb. 12 oz. The head circumference was 12 in. and the shape unchanged. She lay in opisthotonos, pale and convulsing whenever disturbed. Respirations were still irregular and the crowing cry persisted. At this time it was noticed that she had no blink reflex and made no attempt to look at the nursing staff or at dangling objects. Gavage feeding

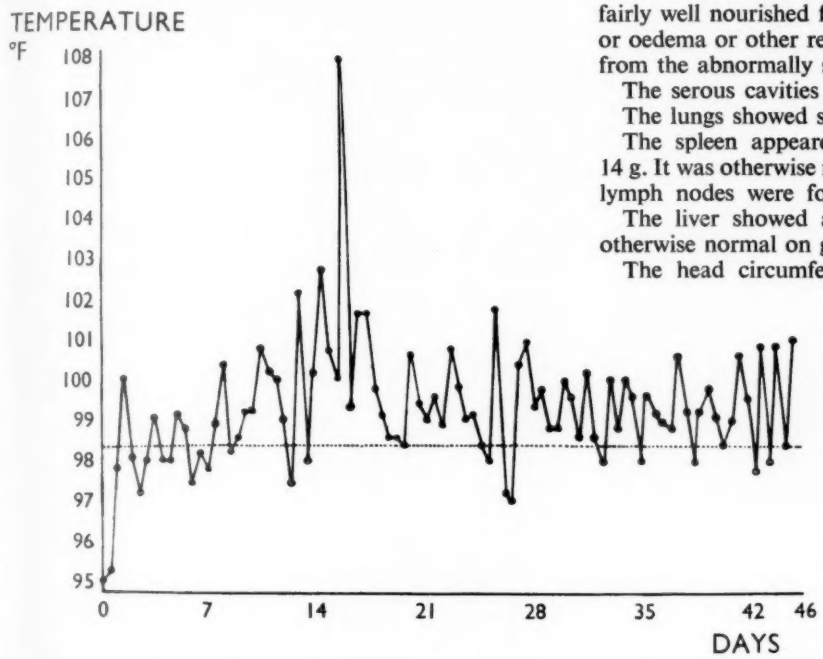

FIG. 1.—The temperature chart.

was still required and had to be continued till death. An examination of the eyes was made on May 5 by Mr. C. A. Brown who reported that there was complete bilateral optic atrophy and almost complete absence of all retinal vessels. The pupils were equal and there was only slight reaction to light.

By May 12 her condition was very much worse, with continuous hiccough and convulsions, despite heavy sedation. She died on May 14 at the age of 7 weeks. Just before death her weight was 5 lb. 8 oz.

Investigations.—In a specimen of cerebrospinal fluid, taken on April 12, there were 6 leucocytes per c.mm., and 145 erythrocytes per c.mm.; the value for protein was 70 mg. % and there was a slight excess of globulin; there was 78 mg. % of sugar; the sample was sterile on culture. The urine on April 9 contained a trace of protein and numerous epithelial cells, yielding a scanty growth of *Bact. coli*. On April 9 the haemoglobin level was 128%, falling to 70% on May 7; the blood urea on the former date was 46 mg. %. A sample of maternal blood was Group O Rh positive and gave a negative Kahn reaction.

Family History.—The parents are both healthy, of English nationality and with no history of Jewish extraction. There is no consanguinity. The father, aged 36, is employed as a saw-mill labourer, has one brother who is a certified mental defective, and an aunt who has been in an institution for 'mental trouble'. The mother, aged 37, has no family history of mental or nervous disorder. The patient was the eighth child in the family, and there has been another sibling since, who is apparently normal and healthy (Table 1).

Necropsy Findings.—Post-mortem examination was carried out 18 hours after death. The body was that of a fairly well nourished female infant showing no jaundice or oedema or other remarkable feature externally, apart from the abnormally shaped head described below.

The serous cavities were normal.

The lungs showed some basal congestion only.

The spleen appeared slightly enlarged and weighed 14 g. It was otherwise normal in appearance. No enlarged lymph nodes were found.

The liver showed acute venous congestion but was otherwise normal on gross examination.

The head circumference was 12 in. The skull was abnormal in shape, the antero-posterior diameter being long and the bi-temporal diameter abnormally short. The vault of the skull was tall and scaphocephalic. The sutures were not united and the anterior fontanelle was not quite closed.

On opening the skull there was found to be a very considerable degree of external hydrocephalus. The brain was very small and firm with a very much simplified convolutional pattern and lay deep down in the base of the skull like a shrunken walnut within its shell, the greater part of the cranial cavity being occupied by cerebrospinal fluid. A skiagram of the head after removal of the fluid (Fig. 2) shows clearly the relative proportions of the brain and the cranial cavity.

TABLE 1
THE SIBLINGS OF M.C.

No.	Date of birth	Sex	Birth weight (lb. oz.)	Subsequent progress
1	20.12.36	M	5	Healthy, attended ordinary school; employed in shoe factory
2	13.5.39	F.	5	Normal, at secondary modern school
3	3.6.40	F.	Unknown	Died at 17 days; amaurotic idiocy (case described by Norman and Wood, 1941)
4	18.6.43	F.	Unknown	Born in hospital, died in first 24 hours. Atelectasis only found, no report on the brain available
5	4.6.46	M.	5 10	Normal, at ordinary primary school
6	23.6.47	M.	6 1	Normal, at ordinary primary school
7	19.4.49	M.	6 14	Normal
8	26.3.51	F.	4 1	The patient, Margaret C.
9	29.11.52	M.	5 2	Normal infant

The brain, fixed in 10% formol-saline, weighed 65 g. (At birth the brain normally weighs approximately 300 g.)

The leptomeninges loosely covered the surface of the firm, shrunken cerebrum, the cerebral vessels being normal in appearance and distribution. The straight, unbranched central sulci were conspicuous, as were

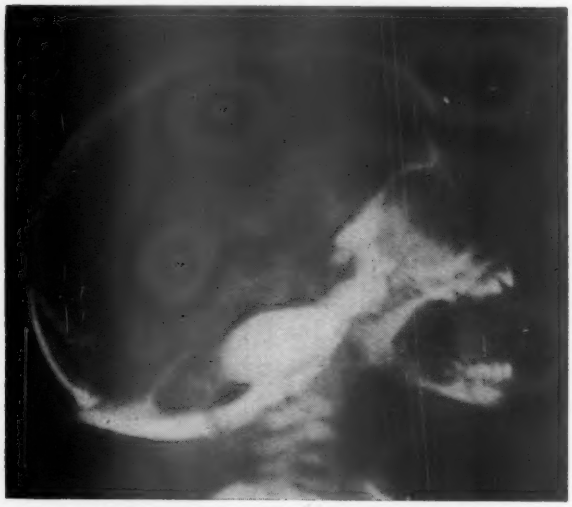

FIG. 2.—Skiagram of skull taken at necropsy, with the brain still *in situ*. The calvarium had been sawn through and replaced.

broad deep calcarine and lateral fissures, the latter leaving the insulae widely exposed. A simple sulcal pattern in the frontal lobes contrasted with more complex fissuring in the parieto-occipital region (Fig. 3).

The cut surface of the cerebrum was rigid and greyish white, appearances being those of an extreme sclerosis. Demarcating the narrow pale cortex (1-1·5 mm. thick), there was a fine, ivory-white line at the cortico-medullary junction, which proved to be particularly rich in lipoids. There was a fine, spongy reticulation of the subcortical white matter, particularly at the summits of gyri. Deeper in the centrum ovale there were occasional creamy-white deposits of lipoid, 1-3 mm. in diameter. The tissue as a whole had evidently shrunk considerably, as was shown not only by its abnormal firmness but also by an almost total absence of further shrinkage during the embedding of blocks from the cerebrum in paraffin wax.

The brain-stem, cerebellum, medulla oblongata and spinal cord were small in proportion to the cerebrum, their cut surfaces being firm and pale. Seen from the side, the cerebellar hemispheres were somewhat flattened. There was an area of total cortical atrophy of approximately 5 mm. diameter on the inferior surface of the left hemisphere loosely covered by leptomeninges (Fig. 3). The other organs of the body showed no abnormalities on naked-eye examination.

Histological Findings.—The following are descriptions of the histology, particularly of the brain and central nervous system.

SPLEEN. The pulp contained numerous large rounded cells with clear outlines, small indistinct nuclei and abundant cytoplasm which contained numerous tiny droplets of weakly sudanophil material giving the whole cell a ground-glass appearance. These cells were found singly and in small groups.

LUNG. There was patchy collapse and bronchopneumonia. Some histiocytic cells containing lipoid were present.

THYMUS. The cortex was normal. The medulla showed a normal number of Hassall's corpuscles. It also contained some rounded opaque cells containing sudanophil lipoid.

KIDNEY. Some lipoid-containing cells were present.

ADRENAL. A number of similar cells were found in the medulla.

CENTRAL NERVOUS SYSTEM.—The central nervous system was examined using frozen sections from blocks taken from the cerebral hemisphere, mid-brain, pons, cerebellum, medulla and spinal cord. The right cerebral hemisphere was used for chemical analysis. Sections from each block were stained with Azur A (*p*H 4) by the Kultschitsky-Pal myelin method, Holzer's glial fibre method, Bielschowsky's neurofibril method and with Sudan III. Various sections were also used for Penfield's combined oligo- and micro-glial method, and for the globus method for astrocytes.

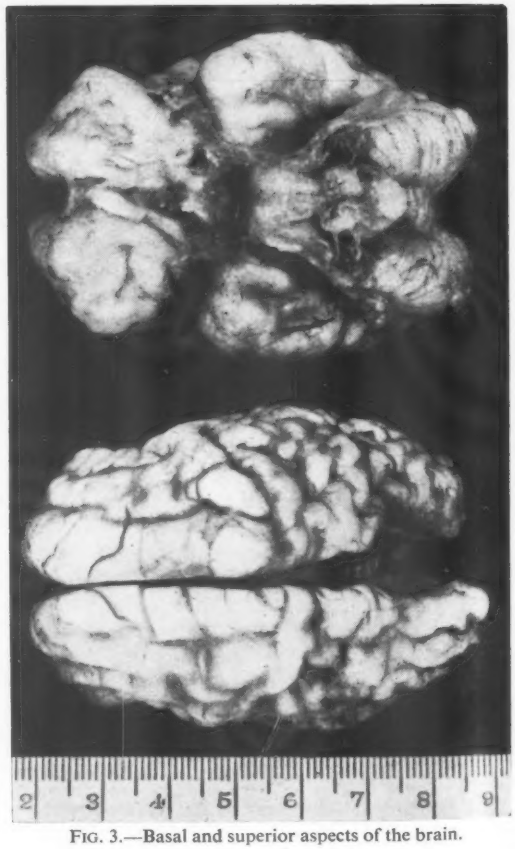

FIG. 3.—Basal and superior aspects of the brain.

Most of the nerve cells in the cerebral cortex showed morphological changes resembling those seen, in this situation, in the earlier forms of infantile amaurotic family idiocy. The cells in question had become 'fossilized'; they were spherical, hyaline or indistinctly granular masses, each containing one or more nuclear remnants, devoid of Nissl substance and no longer recognizable as neurons (Fig. 4). Similarly, enormous numbers of cells throughout the cerebral white matter, no longer recognizable either as normal astrocytes or microglial cells, were distended with lipoid substances. As a consequence of the shrunken state of the tissue, extreme crowding of cortical cells was evident in frozen sections and was scarcely more marked in paraffin-embedded

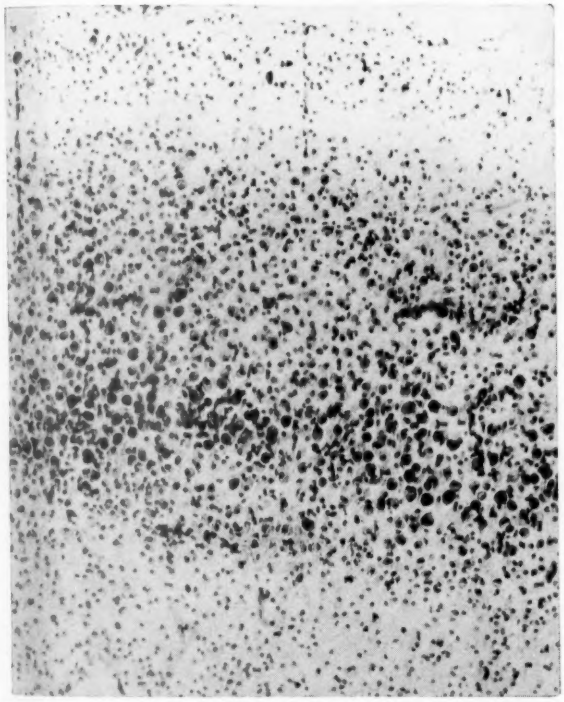

FIG. 4.—Frozen section of the cerebral cortex in the occipital region. Azur A × 80.

ones. Although glial fibrils could not be demonstrated in the cerebral cortex nor in much of the subcortical white matter, staining with aniline blue showed the ground substance of both to consist of a relatively coarse meshwork, to whose presence the unusual rigidity of the tissues may perhaps have been related. It was not possible to demonstrate the presence of morphologically normal astrocytes, nor were attempts to impregnate the microglia successful. Nevertheless, in Nissl preparations, nuclei characteristic of microglial cells were present in apparent excess in the cerebral cortex, white matter and elsewhere, notably in subcortical centres where the more severe type of nerve cell change had occurred, or where there was evidence of nerve cell loss, e.g., in the inferior olivary nuclei. Occasional small rounded nuclei, thought

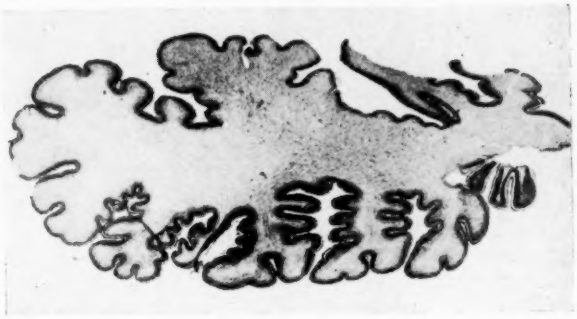

FIG. 5.—Frozen section through the long axis of the left cerebellar hemisphere. Azur A × 1·4

to be of oligodendroglial cells, were seen in those regions of the medulla oblongata and spinal cord where normal myelination had occurred, but not in other situations. The basal ganglia, internal capsule, and thalamus were together the site of a dense glial fibrosis which extended downwards into the substantia nigra and tectal region of the midbrain. A less dense, fairly evenly distributed fibrosis was found involving the pons, medulla oblongata and spinal cord.

THE CEREBELLUM. There was marked atrophy of the cerebellum, affecting the hemispheres (Fig. 5) more than the vermis (Fig. 6) and, in the latter situation, almost entirely sparing the median and flocculonodular lobes. Minimal glial fibrosis accompanied the atrophic changes in the anterior lobe, although the former process was more marked, laterally, in the hemispheres. The more nearly normal parts of the cortex contained unaltered Purkinje cells; most however, showed varying degrees of fatty change, a small proportion having become the rounded hyaline bodies characteristically present in the cerebral cortex. Many Purkinje cells thus severely affected lay in the internal granular layer and in a small heterotopic area of grey matter in the flocculonodular lobe. In the anterior lobe, sparseness of cells in all three layers of the cortex, with absence of Purkinje cells at the tips of the atrophied folia, contrasted with more nearly normal appearances of the cortex bordering the depths of

FIG. 6.—Frozen section, in the sagittal plane, through the vermis of the cerebellum. Azur A × 5

the fissures. Cells in the dentate nucleus showed marked fatty changes, although they were still recognizable as neurons.

CEREBRAL CORTEX. Within the cerebral cortex there was a relative sparing of nerve cells in certain areas: a few large pyramidal cells in the fifth layer of the precentral cortex (area FA) although much shrunken, still retained their neuronal structure; in the insular region there were numerous Cajal cells lying on the outer side of a dense plexus of fibres in the outer molecular layer, and the fifth layer also contained occasional surviving pyramidal cells; in the pyriform cortex, particularly in its forward extension onto the gyrus semilunaris, many neurons were relatively little damaged. On the other hand, definite evidence that nerve cells had disappeared during the course of the disease was not obtained except in the pyramidal cell layer of the cornu ammonis, where a dense glial fibrosis marked the site of an outfall of cells.

OTHER CENTRES. There was neuronal damage, comparable to that seen in the cerebral cortex, with varying degrees of nerve cell loss and gliosis, in the corpus striatum, subthalamic region, red nucleus, pontine and olivary nuclei. In the last-named group, the dorsal accessory nucleus (related to the vermis of the cerebellum) showed better preserved nerve cells and less marked gliosis than was seen in the main olivary nucleus. The medial and lateral geniculate bodies showed severe changes, as did the greater part of the thalamus. The lateral nuclear mass of the thalamus, however, contained numerous large cells which, although distended with lipoid, were recognizable as neurons and lay in an apparently normal neuropil. A radiation of fine unmyelinated fibres passed from the anterior part of this region into the cortical white matter of the more posterior part of the frontal lobe, although very few of these fibres reached the cortex. Nerve cell morphology was fairly well preserved in the hypothalamic region.

Nissl substance and intracytoplasmic neurofibrils, associated with an apparently normal neuropil, were demonstrable in motor cells from the occulomotor nuclei to the anterior horns of the spinal cord. The motor cells, however, as well as nerve cells related to afferent systems, for example, in the posterior horns, the posterior column nuclei and nuclei of sensory cranial nerves, almost without exception contained large single accumulations of lipoid. Nerve cells in Gasserian ganglion also showed these changes.

CRANIAL NERVES. The optic nerves were thin, heavily gliosed and contained no more than occasional non-medullated axones. The olfactory nerves were unmyelinated. The remaining cranial nerves showed no specific abnormalities.

MYELINATION. On comparing the following findings with those of Langworthy (1933) in human prenatal and neonatal material, it was evident that there had been a general retardation in the maturation of the brain and spinal cord. Interpretation of the histological picture was complicated by the poverty of myelinated fibres in parts of the cerebrum and cerebellum where myelin is normally deposited before birth, but which, in this instance, showed particularly severe pathological changes.

No more than occasional thickened and distorted myelinated fibres were detectable microscopically in the corona radiata, internal capsule, crus cerebri and in the ventrolateral region of the thalamus. Similarly, sparse myelination was seen in the fibre capsule of the subthalamic nucleus and in the red nucleus. On the other hand the heavily gliosed globus pallidus, normally well myelinated in the 8-month-old human foetus, contained no neuropil and was practically unmyelinated. At a single level in the midbrain, extremely scanty microscopically visible myelination could be identified in the occulomotor nerve, commissure of the inferior colliculus, tectospinal fibres, brachium conjunctivum, lateral spinothalamic fibres and medial lemniscus. Myelination of pathways in the pons was heavier than in the midbrain, and in the medulla and spinal cord, more complete than in the pons. The intracranial portions of the cranial nerves, from the third nerve onwards, were well myelinated, as was the fibre capsule of the inferior olivary nucleus and the reticular substance in the medulla. There were a few very thinly myelinated fibres in the pyramidal tracts, although non-myelinated fibres appeared to be more numerous. A number of well myelinated spino-cerebellar fibres entered the superior and inferior peduncles, which were otherwise non-myelinated, as was the middle peduncle. In the vermis of the cerebellum the whole of the white matter was thinly myelinated, although in the hemispheres very scanty myelination was confined to those folia, mainly on the inferior surface, exhibiting a relatively less severe degree of atrophy. Myelination in the cervical region of the cord with the exception of a marked retardation in the posterior columns, was at about the stage of completion normally reached at birth (Fig. 7).

Histochemical Findings.—It was possible to perform a limited number of histochemical tests on frozen sections of the formalin-fixed brain tissue.

Large, single, intracytoplasmic globules of strongly sudanophilic substances were found in glial cells, evenly distributed throughout the cerebral white matter, with occasional small dense focal aggregates. This substance was readily soluble in alcohol and was thought to consist

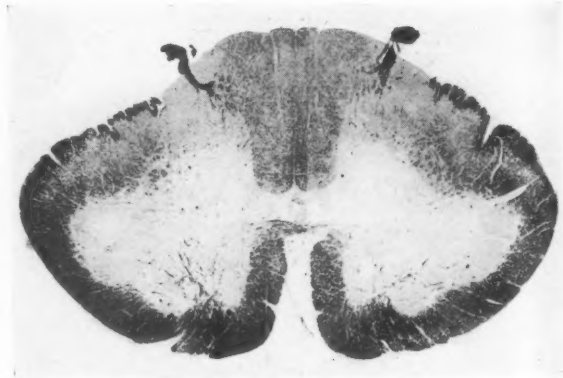

FIG. 7.—Transverse frozen section through the cervical enlargement of the spinal cord. Kultschitsky-Pal method for myelin sheaths × 2·8.

of neutral fat. There were also small needle-like crystals, some lying extracellularly, others within globules of neutral fat; they stained lightly with osmic acid, gave a play of colours with equal parts of acetic and sulphuric acids and were readily soluble in alcohol and other solvents. No change followed treatment with digitonin, although occasional Maltese cross forms were seen with polaroid lenses on heating sections to 56° C. and re-cooling. The crystalline material was thought to consist of cholesterol and/or its esters. Lipoid in the white matter stained with haematoxylin in the Kultschitsky-Pal myelin method after mordanting for periods of up to 48 hours; after more prolonged mordanting it became progressively less deeply stained, in this respect resembling normal myelin.

Unlike the glial cells in the white matter and in the cortex nerve cells in the latter situation were only faintly sudanophilic and still retained a faint propensity for staining with Scharlach R after immersing the sections in acetone, ether, pyridine, ethyl alcohol and boiling chloroform. The residual material was basophilic, gave a positive periodic acid-Schiff reaction, had a marked affinity for aniline blue and cresyl violet and showed faint acid-fast staining with carbol-fuchsin. With prolonged mordanting, the lipoid in cortical nerve cells stained progressively more darkly after 48 hours, reaching maximal intensity after four to five days. In this respect the staining of intraneuronal lipoid differed from that of fatty material in the white matter, although resembling the behaviour of erythrocytes within cortical blood vessels

Chemical Analysis of Formalin-Fixed Cerebrum.—Quantitative chemical estimations were made of one cerebral hemisphere from case M.C. (Table 2) and of a control neonatal case by Mr. A. H. Tingey. In both instances the brain had been in 10% formalin for approximately one year. Certain results showed significant departures from normal values. The presence of an excess of cholesterol is in accordance with the histological findings. Estimation of phosphatide in formalin-fixed brains is liable to give erroneous results due to the occurrence of hydrolysis. Thus the low value obtained for M.C. might not be due entirely to the poverty of myelin in the cerebrum. Values obtained for phosphorus in the lipoid extracts were thought to give some indication of the nucleoprotein content of this tissue. The significance of the low value obtained for M.C. is not clear.

TABLE 2

CHEMICAL ESTIMATIONS

	% Cholesterol in Dry Extract	% Phosphatide	% P in Lipoid Extract	% H_2O
M.C.	15·3	7·6	0·333	82·8
Neonatal Control ..	4·2	19·5	0·630	89·7

Discussion

The clinical features of this case are of some interest. The abnormal appearance of the skull, which was recognized almost from birth, suggested that some degree of craniostenosis was present which might be associated with microcephaly or other maldevelopment. This possibility was greatly increased by the discovery of abnormal fundi oculi in the fifth week of life. An altered respiratory pattern was perhaps the most striking and constant clinical feature, the irregular gasps and periods of apnoea indicating that there was little control of the medullary and pontine functions by higher centres of the brain. These observations, in conjunction with the picture of decerebrate rigidity which developed, made the diagnosis of a gross brain lesion certain. In the elder sibling (Norman and Wood's case), feeding difficulty was the chief symptom. It is therefore worthy of note that in the present case sucking and swallowing reflexes were completely absent throughout the seven weeks of the child's life, and only very skilled nursing kept her alive so long and even enabled normal general bodily growth.

The occurrence of this disorder twice in a large family of otherwise healthy siblings suggests that, as in Tay-Sachs and Gaucher's disease, it is determined by the presence of a recessive gene. The two main theories advanced to explain the production of Tay-Sachs disease are: (1) that it is primarily a disorder of lipoid metabolism; (2) that the 'hyaloplasm' of nerve and glial cells has an inherent tendency to become loaded with fatty substances (Schaffer, 1930). In support of the first hypothesis must be mentioned the occurrence of small lipoidal deposits in macrophages outside the central nervous system, as was described by Bielschowsky (1928) and as has been seen in the two congenital cases. Similarly, Klenk's identification (Klenk, 1939, 1941) in the tissue of a lipoidal substance, supposedly not present in any appreciable amount in healthy central nervous tissue, has also been advanced in support of the former theory. It is unfortunate that in neither congenital case has it been possible to study Klenk's compound in the formalin-fixed tissue. In the present case the finding of an excess of cholesterol is of interest, although this substance is deposited in many degenerative conditions of the brain.

An increased consistency of the brain in Tay-Sachs disease has often been noted. The brain at necropsy may be rubbery, as in a case described by Baker and Platou (1938). In both congenital cases there was a marked change in the physical state of the brain. Histological differentiation of nerve centres and myelination of fibre tracts had, nevertheless, already

begun. It appeared, therefore, that some catastrophic event, perhaps involving dehydration of the ground substance, with consequent shrinkage of the tissue, had occurred during the last months of pregnancy.

The pathological findings were of particular interest in relation to the selective vulnerability of certain centres. As not infrequently occurs in infantile amaurotic familial idiocy, there was marked atrophy of the cerebellum in both congenital cases. In the present case the size and degree of differentiation of the cerebellar vermis corresponded closely with that of a normal 230 mm. embryo, that is one of 28 to 32 weeks' gestation (Hochstetter, 1929). A comparable vulnerability of the cerebellum at a late stage in its development has been demonstrated by Hicks, Schaufus, Williams and Cooney (1952), who obtained cerebellar defects in mice which had been submitted to ionic radiation during the last few days of intra-uterine life.

In the cerebral cortex, studies by Vogt (1929) and earlier authors showed that although the nerve cell changes in amaurotic family idiocy are generalized, there are variations in the presumed rapidity with which cells succumb, in the intensity of the neuroglial reaction and in the degree of vascularity in different cortical areas. Nerve cell changes in the cerebral cortex in each of the two congenital cases were more severe than are usually seen in the infantile form of the disease. The survival of occasional structurally recognizable large pyramidal cells in the fifth layer of the precentral region is of some interest, since the latter are among the earliest cortical neurons to undergo histological differentiation. Findings in the cerebral cortex were therefore also in accordance with the view that the foetal brain had sustained damage at a late stage in its development.

Summary

A second case of congenital cerebral lipoidosis is described in a younger sibling of a case reported by Norman and Wood (1940). The present infant, also a girl, was recognizably microcephalic at birth and survived for six weeks. The histopathological changes in the central nervous system, almost identical in the two cases, have a general resemblance to those of infantile amaurotic family idiocy. An excess of cholesterol was found in the white matter. Following prolonged extraction with solvents, an insoluble Schiff-positive lipoidal residue remained within the cytoplasm of nerve cells of the cerebral cortex and elsewhere.

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MONGOLISM IN BOTH OF MONOZYGOTIC TWINS

BY

ROBERT J. YOUNG

From the Department of Child Health, Queen's University, Belfast, and the Belfast City Hospital

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Mongolism in more than one member of a family is a rare event; mongolism in both of twins is even rarer and merits interest. Warner (1949) collected from the literature two families, each having four mongoloid siblings, and four families, each having three mongoloid siblings, and 42 families each having two mongols per family. He mentioned two cases of special interest, (Lahdensuu, 1937; Sirkin, 1937) in which each mother, after having a series of normal children, had two successive children with mongolism by different fathers. Excluded from the data were families in which mongols constituted one or both of twins. In addition he collected from the literature data on 101 sets of twins in which one or both members were affected. He added a case of mongolism in one of twins and in another sibling. An analysis of these 102 authenticated cases of mongolism in twins showed 30 cases of unlike-sex twins in which one was affected, 15 cases of unknown sex in which one was affected, 37 cases of like sex in which one was affected, and 20 cases of like-sex twins in which both were affected. Of this latter group Warner considered that 10 sets of twins were monozygotic.

It was, however, often uncertain whether the twins were mono- or dizygotic and it is interesting that up to the present mongolism in both twins of different sex has not been described.

Subsequent to Warner's comprehensive review further cases of mongolism in one of twins have been recorded by Crozier and Campbell (1950), Cook (1950) two cases, Dawson (1950), Brown (1950), Graham (1950), Posteraro (1951), Robertson (1952), Engler (1952) three cases, Morris and MacGillivray (1953) and Lang-Brown, Lawler and Penrose (1953) three cases.

Bencini (1952) and Lang-Brown *et al.* (1953) have reported instances of mongolism in both members of a monozygotic twin pair.

The purpose of this communication is to put on record an additional example of a pair of apparently monozygotic twins in which both members were affected by mongolism.

Case Report

There was no consanguinity in the family pedigree and no knowledge of the presence of mongolism in the family on either side. The father, aged 45 years, was alive and in good physical and mental health. The mother, aged 29 years, was a twin. She had had scarlet fever, measles and mumps in childhood but otherwise had been free from illness. The mongol twins reported here were the result of a second pregnancy during which her health was good. A first pregnancy, three years previously, had resulted in the birth at full term of a normal 9 lb. male infant, still alive and healthy. There was no history of stillbirths or miscarriages.

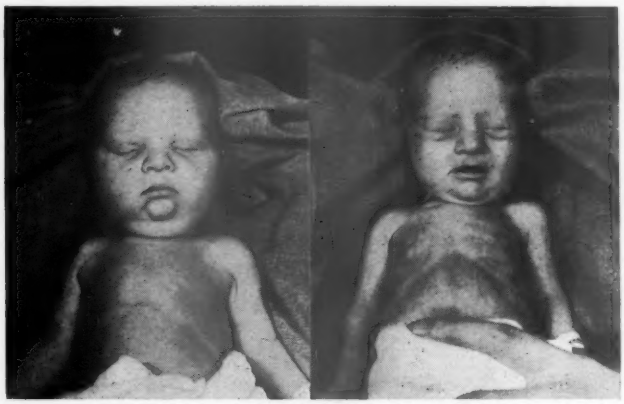
She was admitted to the Jubilee Maternity Hospital as a case of twin pregnancy, the membranes having ruptured 24 hours before admission. The amniotic fluid was stained bright red but the patient, a qualified midwife, insisted that the loss was bloodstained liquor and not a haemorrhage. She was well nourished and clinical examination revealed no signs other than those expected at a 36 weeks' pregnancy. After a labour lasting three and a half hours she gave birth to twin boys weighing 4 lb. 12 oz. and 3 lb. 4 oz. respectively. There were two separate placentas.

Examination showed that each infant had the characteristic appearance of mongolism; oblique palebral fissures, marked over-development of the epicanthic folds, and a tongue which was frequently protruded. Each child had blue irides with numerous white spots. The hands were short and the fifth digits short and incurved. The palms and soles showed the markings considered to indicate mongolism. Both twins showed a facies typical of mongolism, and all who saw them had no doubt that the diagnosis of mongolism was correct. Though each twin had the characteristic stigmata of mongolism they were not identical in appearance as may be seen from the photograph taken on the fourth day of life (Fig. 1).

At birth, the first twin (*a*) weighed 4 lb. 12 oz. and measured 17½ in. in length. The colour was fairly good. On the third day of life the infant became jaundiced, was drowsy and had to be fed by tube. On the tenth day drowsiness and jaundice were marked, but on the fifteenth day the infant became a little brighter and by the eighteenth day was feeding fairly well from a baby-type feeder. On the twenty-second day the jaundice began to clear and this had completely disappeared on the thirtieth day by which time the infant was feeding well from a bottle. The baby continued to gain weight steadily

and was discharged home aged 7 weeks. No cardiac murmur or other evidence of a cardiac lesion was detected at any time during this period. The child developed pneumonia and died when aged 8 months. A necropsy was not carried out.

At birth, the second twin (*b*) was 3 lb. 14 oz. and measured 17 in. in length. There was blue asphyxia but on admission to the nursery his general condition was only fair. On the second day of life melaena was present. At this time a systolic murmur was audible over the praecordium with maximum intensity at the third left intercostal space. The second pulmonary sound was accentuated and split. A systolic thrill was palpable at the site of maximum intensity of the murmur. On the third day the infant became jaundiced and his general condition was weak. Jaundice deepened, the general condition deteriorated, and he died on the seventeenth day.



A B

FIG. 1.—The twins, showing dissimilar facies.

A necropsy showed congenital heart disease, with a widely patent foramen ovale and patent inter-ventricular septum; pulmonary congestion, oedema and focal atelectasis; and persistent extra-medullary haemopoiesis of the liver and spleen.

Evidence of Monozygosity.—It is known that 20-30% of monozygotic twins are born in dichorial placentas so that the knowledge that there were two distinct placentas at birth is valueless. To be of any value in determining zygosity the foetal membranes, even when fused, 'must be properly examined grossly and microscopically and with adequate tissue sections' (Morison, 1949). In the presence of two separate placentas it is only possible to make a comparison of blood groups, hair colour, skin colour and texture, irides colour, prints of the palms and soles, and the general features.

Detailed blood group studies (Table 1) showed complete concordance between the twin blood groups but some dissimilarities between the blood groups of the father and the mother. This was taken as conclusive evidence that the twins were monozygous.

The colour of the hair, eyebrows and irides, and the skin colour and texture of both twins were similar. The first twin was ½ in. longer, 1 lb. 8 oz. heavier, and more round-faced than the second twin. It is known, however, that like twins may differ in size at birth, and Schatz (quoted by Newman, Freeman, and Holzinger, 1937, and referred to by Morison, 1949) found that at about the middle period of pregnancy the size difference in monozygotic twins was greater than at term. The difference in general features of the twins, which were premature, is therefore not significant.

Electrocardiograms showed no significant dissimilarities. In the second twin, with clinical signs of a congenital heart lesion, SI and AVL were marked, and R VI suggested right ventricular preponderance. T was flat in limb leads. The R segment of VI was late but the total duration of the QRS group was only 0·8 second, so there was no bundle branch block. In the first twin, without any abnormal clinical signs in the cardiovascular system, differences in electrocardiogram were minor, namely, there was better voltage in T VI but the voltage of T in limb leads was low, and there was similar right ventricular predominance.

The presence of a congenital heart lesion in only one of the twins is not evidence against the twins being monozygous, as instances of congenital heart disease in one of monozygotic twins have been reported. Weitz (1936) reported patent ductus arteriosus in one of monozygotic twins, and Forsyth and Uchida (1951) noted an auricular septal defect in one of uniovular twin girls. Morison (1949) presented convincing evidence that congenital malformations may occur in one of monozygotic twins.

TABLE 1

BLOOD GROUPS OF TWINS AND PARENTS

Sera Used	ABO Group	C^w	C	D	E	c	e	Most Probable Rh Geneotype	M	N	S	Le^a	P
1st Twin	A_1B	–	–	–	–	+	+	rr cde/cde	+	–	+	–	–
2nd Twin	A_1B	–	–	–	–	+	+	rr cde/cde	+	–	+	–	–
Father	B	—	+	+	–	+		R_1r CDe/cde	+	+	+	–	–
Mother	A_1	–	–	–	–	+		rr cde/cde	+	(+)	+	–	+

The palm and sole prints of the twins (Fig. 2) were made on the eighth day of life. The characteristic trends elucidated by Cummins (1939) as being distinctive of mongols were present in both twins. In addition, the homologous hands and feet of the twins were more nearly alike in pattern than the two hands or two feet of either twin.

> 'It is generally accepted as a criterion of monozygotic twinning that the difference between the right and the left hand of either twin should be greater than the difference between the two corresponding hands of the pair of twins' (Ford and Frumkin, 1942).

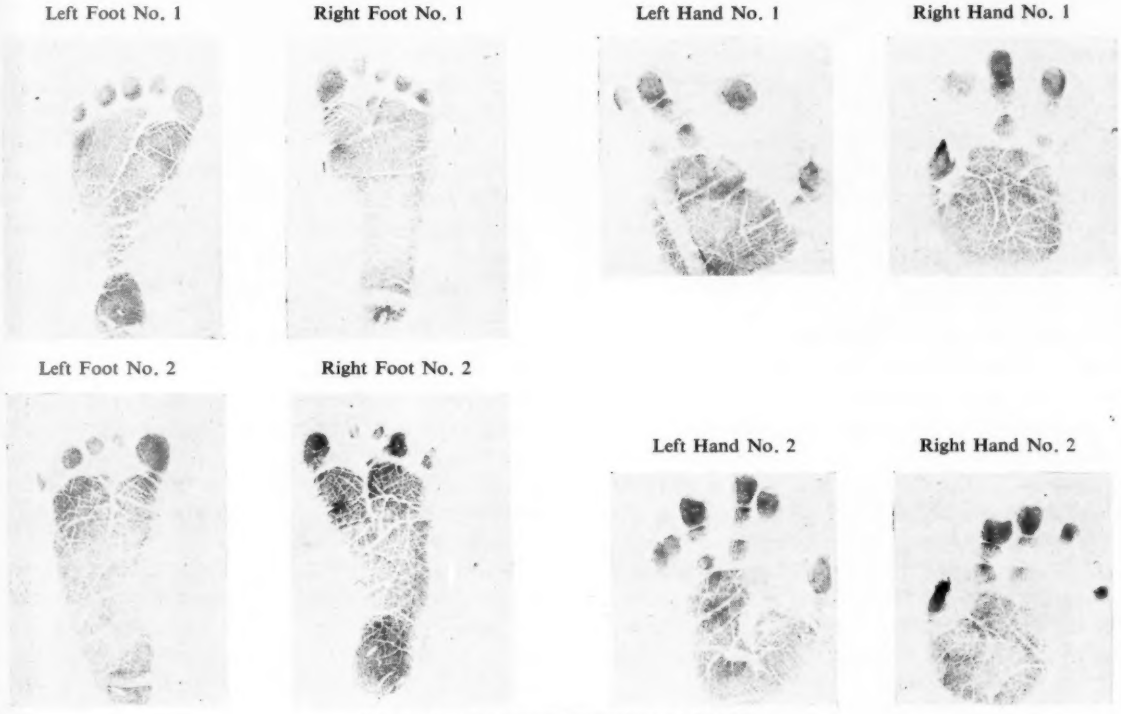


FIG. 2—Foot and hand impressions of the twins.

Detailed digital, palmar and plantar formulae could not be obtained, as in the early neonatal period the papillary ridges are not sufficiently raised to hold a thin film of ink and there is no known method of obtaining a satisfactory impression of the ridge system in this age period.

The evidence, based on blood typing, that the twins were monozygous was thus collaborated by the studies of the dermatoglyphic patterns and the colour of the hair, eyebrows and irides of the twins.

Discussion

Intrapair variations in dizygotic twins may be due to both heredity and environment, but environment only can be responsible for intrapair variations in monozygotic twins.

The occurrence of a congenital heart lesion in one of monozygotic twins provides another example of the influence of intra-uterine environment on the development of congenital malformations.

That only one twin had a congenital heart lesion is in keeping with the mechanism of production of congenital malformations put forward by Morison (1949). From a detailed study of two sets of monozygotic twins, in which congenital malformations occurred in only one twin in each set, he concluded that 'since the genetic inheritance of the malformed twin should be similar to that of its normal partner, the malformations arise from an arrest of normal development when the placenta of one twin is at some environmental disadvantage in obtaining nutrition from the utero-placental site for a short period early in intra-uterine life'. That there was unequal sharing of nutrient may be deduced from the twin with the congenital heart lesion being 1 lb. 8 oz. lighter than the twin with a clinically normal heart. Morison was careful to point out that while environment may be a cause of congenital malformation, there are other causes.

The occurrence of mongolism in both of monozygotic twins makes pertinent a study of the causation of mongolism.

From a study of the ages of the mothers of 2,822

mongols, Bleyer (1938) compiled evidence that maternal age is a significant aetiological factor, the peak age of the mothers in his series being 41 years. However, normal children have been born in families both before and after the birth of a mongol child, and Tredgold (1952) gives an instance of a mongol child being born to a girl aged 16 years. The age of the mother, therefore, is not the sole determining factor.

A pituitary or thyroid imbalance in the mother was suggested by Benda (1949) to be of importance in the production of mongoloid infants. In a series of 50 patients he found a degree of thyroid disorder in over one-third of the mothers. He did not, however, define his criteria of thyroid disorder. He mentioned three patients in whom there was a high basal metabolic rate and an overactive thyroid, and in another case he noted 'thyroid deficiency suspected'. It seems extremely unlikely that mongolism could be produced by either an excess or deficiency of thyroid secretion. Furthermore, any theory of endocrine imbalance would not explain why mongolism has occurred in only one of 97 sets of twins.

The nidation theory postulates that the lesion occurs after fertilization during implantation of the ovum (Bennholdt-Thomsen quoted by Jervis, 1943). The division of the embryo into twin cell groups, however, has already occurred when implantation takes place. Therefore, if this theory were true, and the aetiological factors entirely environmental, the incidence of discordant monozygotic mongol twins should equal the incidence of discordant dizygotic mongol twins. Many instances of discordant dizygotic mongol twins have been reported but no instance of discordant monozygotic mongol twins has yet been reported.

Complete concordance of monozygotic twins and discordance of a high number of dizygotic twins are inconsistent with the hypothesis that mongolism is due to exogenous agents acting in early embryonic life.

The mutation theory (Bleyer, 1934) is consistent with the presence of concordance in monozygotic twins and discordance in dizygotic twins. Warner considered that of the 20 sets of concordant twins reviewed by him, 10 were dizygotic. It would have to be assumed that mutation, which is a rare occurrence, has taken place in two different ova at the same time, in the same place and in 10 instances, a highly improbable assumption (after Jervis, 1942). It should be pointed out that the 10 pairs of dizygotic concordant twins were of the same sex type when it would be expected that about half should be of different sex. In accounts of some of those twins an inadequate analysis of the type of twinning was made so that the number of monozygotic twins may be higher than that accepted by Warner.

The genetic hypothesis (Macklin, 1929) assumes that mongolism is due to an alteration of the chromosomes recessively or dominantly inherited. This is consistent with the finding of concordance in monozygotic twins and non-concordance in dizygotic twins and also with the finding of a certain number of concordant dizygotic twins. The only real evidence, however, in favour of an explanation involving transmission of a gene is that although mongolism is uncommon, it is more common in siblings than in the general population. If this is to be explained on a genetic basis then the gene must very often be non-penetrant, that is, present but not exerting its effect. Otherwise one in four or one in one of siblings would be affected or unaffected. Therefore on such a hypothesis it would not be very surprising if there were many pairs of monozygotic twins where only one was affected.

Penrose (1946, 1951) discussed the possibility that mongolism could be partly determined by some unknown antigenic factors. The same author, working with Lang-Brown *et al.* (1953), subsequently carried out detailed blood typing of 148 cases of mongolism and their parents and siblings. They concluded that mongolism could not be due to antigenic incompatibility between mother and foetus within the known blood group antigen-antibody systems.

Halbertsma (1923) was the first to suggest that mongolism is germinal in origin and not acquired by the foetus. Jenkins (1933) postulated a plasmatic defect of the germ cell. He concluded that 'in the population of ova there is continually a certain mortality rate. In a period between that of complete viability and failure of reproductive function ova pass through a mongolian-genetic stage'. Fertility diminishes as the age of the mother increases. Jenkins related this diminished fertility to a diminished reproductive viability of the ova. This theory would appear to be the one most consistent with the data on mongolism in twins and with the increasing incidence of mongolism in the older age group of mothers.

Summary

A case history of mongolism in both of twins is recorded. Though the placentas were separate the evidence from blood groups, prints of the palms and soles, hair colour, skin colour and texture, and colour of the irides strongly suggested that the twins were monozygotic.

The data on mongolism in twins and the increasing incidence of mongolism in the older age group of mothers support the hypothesis that mongolism is germinal in origin.

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HEPATIC NECROSIS IN DISSEMINATED HERPES SIMPLEX*

BY

R. C. B. PUGH, G. H. NEWNS and J. A. DUDGEON

From The Hospital for Sick Children, Great Ormond Street, London

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Infection with herpes simplex virus is extremely common and the primary infection is frequently asymptomatic, as is shown by the high proportion of the adult population who possess herpes antibody but yet give no history of the clinical disease. In the symptomatic form, characterized by the appearance of a vesicular eruption on the skin or mucous membranes, considerable variation is seen both in the site and extent of the eruption, as well as in the severity of the accompanying constitutional reaction. Typically the infection is self-limiting and, even in the more extensive forms, recovery is usually complete in two or three weeks with the development of active immunity.

In generalized herpes simplex secondary lesions appear on the skin or mucosal surfaces as the result of dissemination of virus from the initial site of infection. In addition to direct spread on the surface which accounts for some of these lesions, particularly in eczematous patients, there is potent clinical evidence to support the view of spread by the blood stream. Laboratory evidence of viraemia, on the other hand, is fragmentary as the virus has only rarely been recovered from the blood stream (Ruchman and Dodd, 1950; Dudgeon, 1952; McNair Scott, Coriell, Blank and Burgoon, 1952).

There seems little doubt, however, that haematogenous spread is primarily responsible for an atypical form of disseminated herpes that has recently been reported from the United States by Zuelzer and Stulberg (1952). Their eight fatal cases fall into two groups; five newborn infants who were found to have widespread herpetic lesions in the viscera, and three older infants with less extensive visceral involvement. In both groups focal necrotic lesions were a prominent feature in the affected viscera and were invariably found in the liver. Essentially similar hepatic lesions in premature infants were described by Hass (1935), who suggested on morphological grounds that herpes virus was the causative agent, and by Quilligan and Wilson (1951), who recovered herpes virus from the liver in their case.

The case reported here is of an infant who died at the age of 6 weeks after a protracted, though initially mild, illness. At necropsy there was extensive focal necrosis of the liver from which herpes simplex virus was recovered.

Case Report

C.B. was the second child of Italian parents, and was born one week prematurely after a pregnancy that had been complicated by mild maternal toxaemia. Delivery was normal and her birth weight was 6 lb. 13 oz. The immediate post-natal period was uneventful except that a number of small 'spots' were found on the skin on the fourth day of life; they were not vesicular and disappeared within 24 hours.

At the age of 7 days soreness of the tongue and inside of the mouth was noted and this progressed to such an extent that breast feeding had to be discontinued on the twenty-first day. On the twenty-sixth day choking attacks with slight cyanosis occurred after each feed and the family doctor, noting some white patches in the mouth, diagnosed thrush. The child was first seen in the Casualty Department of The Hospital for Sick Children at the age of 27 days; she had a hoarse cry, the tongue was reddened, especially at the tip, but there was no evidence of thrush or ulceration of the tongue or buccal mucosa. She was thought to have had a recent stomatitis and a congenital deformity of the larynx was suspected. Five days later the infant was seen in the Out-patient Department because of a cough which had developed soon after her first attendance at the hospital; the choking attacks had ceased and feeds had been taken well, although she vomited small quantities of clear fluid between feeds. The baby had lost 1 oz. in weight and looked slightly dehydrated; there was a hoarse cry with marked inspiratory stridor and the tongue was still reddened but there was no evidence of thrush or ulceration of the buccal mucous membrane. She was admitted to hospital on the thirty-second day of life.

On examination after admission the infant was pale and a large quantity of mucus continually dribbled from

* This case was reported to the Pathological Society of Great Britain and Ireland on January 3, 1953.

the mouth. Her temperature was 99° F., pulse 126 per minute, weight 7 lb. 13 oz. The tongue and buccal mucosa were uniformly reddened and there were a few small white patches on the palate. *Streptococcus viridans* and coagulase-positive staphylococci were cultured from the mouth but no monilia were isolated.

Local treatment with gentian violet and merthiolate produced an improvement in the oral lesions; the white patches disappeared but the buccal mucosa remained reddened. Feeding was difficult and on several occasions tube feeding was necessary. The weight remained stationary, but for the first eight days after admission there appeared to be no cause for anxiety. On the ninth day her condition suddenly worsened and the temperature rose to 100·4° F. She became cyanosed and numerous haemorrhagic lesions, some of which developed into abscesses from which *Ps. pyocyanea* was isolated, appeared on the limbs. Signs of a left-sided pneumonia developed. Systemic treatment with penicillin, streptomycin and chloromycetin was begun immediately, but there was steady deterioration in her condition and she died two days later, at the age of 42 days.

The mother and father were both healthy and gave no history of herpetic infection; there was no evidence that the mother had been exposed to herpes virus during her confinement.

An elder sibling died in this hospital in 1950 at the age of 3 months; the post-mortem diagnosis was interstitial pneumonitis, lung abscess and bronchiectasis following unresolved neonatal pneumonia. All the available histological material has been re-examined but there is no evidence that herpes virus was responsible for any of the changes found.

Post-Mortem Appearances

The necropsy was performed 44 hours after death. The body was that of a female infant in moderately good nutritional condition with pitting oedema of both legs below the knee (height 21½ in., body weight, 7 lb.). There were many rounded or irregularly shaped macular lesions on the skin of the legs, forearms, hands and left cheek; the majority were small (0·2-0·3 cm. in diameter) and were reddish-purple or brown, but several measured up to 1·5 cm. in diameter and had a yellowish central zone which was surrounded by a reddish-purple halo.

The mucous membrane of the tongue, uvula and pharynx was uniformly smooth, pale and intact; the submucosa of the uvula and pharynx was thickened and oedematous. The oesophageal mucosa was diffusely congested but appeared intact. The liver weighed 200 g. and the capsular surface was studded with numerous yellowish nodules of varying size (Fig. 1); the smaller ones were rounded, 0·2 or 0·3 cm. in diameter, slightly raised above the surface and were often surrounded by a narrow zone of intense congestion. The larger lesions were up to 1·0 cm. in diameter, and many had an irregular

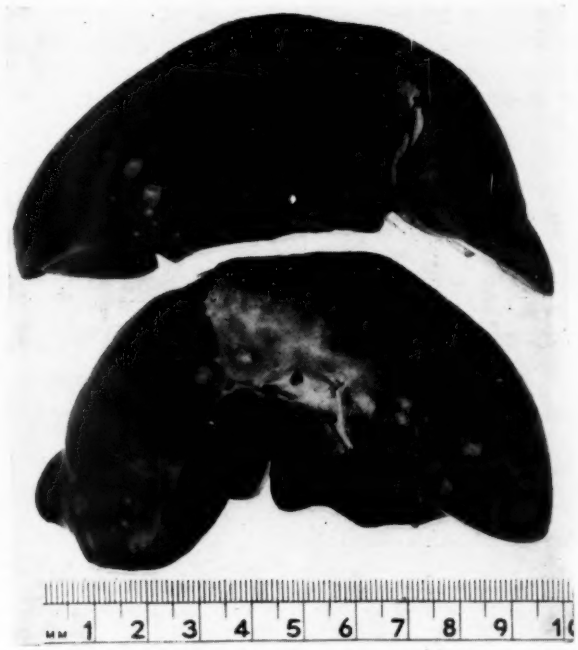

FIG. 1.—External surface of the liver: the necrotic lesions are widely scattered throughout both lobes and vary considerably in size.

outline and were slightly depressed centrally. The diaphragm and omentum also contained rounded necrotic foci which were attached to the necrotic areas on the surface of the liver by fibrinous adhesions. On section the liver parenchyma was swollen and congested and both lobes contained many widely scattered yellow lesions, similar to those seen on the capsular surface. The heart was of normal size but the myocardium was paler than normal. The larynx was normal. The bronchi were diffusely congested and all lobes of both lungs showed numerous subpleural petechiae, while the parenchyma was oedematous and congested with scattered areas of collapse and early bronchopneumonic consolidation. The brain weighed 479 g. and showed considerable parenchymal oedema. Bisection of one of the larger skin lesions revealed a central necrotic core in the dermis and subcutis with congestion of the overlying epidermis. No other abnormalities were found on naked-eye examination.

A heavy growth of *Ps. pyocyanea* was obtained from a specimen of blood taken one hour after death.

Laboratory Investigations

The outstanding feature at necropsy was the presence of the abscess-like areas in the liver. Although it was known that pyaemia was present, it was felt that a more detailed examination of the

necrotic liver tissue might prove of value, particularly as it was noticed that the lesions were remarkably similar to those reported and illustrated by Zuelzer and Stulberg (1952).

Materials and Methods

The essential details of the methods used have been summarized by Dudgeon (1951); the general scheme adopted in this case was as follows:

MICROSCOPY.—A series of smears on clean glass slides was made from a representative area of necrosis. The films were air dried and stained by Gram and Giemsa's methods.

CULTURE.—The liver tissue was cultured aerobically and anaerobically. A 20% suspension of necrotic tissue was prepared in 10% broth saline containing 100 units of chloramphenicol per ml. The suspension was centrifuged at 3,000 r.p.m. for 30 minutes before inoculation.

SEROLOGY.—Blood was collected by cardiac puncture. The serum after separation was grossly haemolysed.

Results.—The results of each investigation are as follows:

MICROSCOPY.—The direct smears showed a relative absence of leucocytes and bacteria in the necrotic liver tissue which suggested that the lesions were not pyaemic in nature. This was substantiated to some extent by the finding of degenerative nuclear changes in the hepatic cells. No intranuclear inclusions were seen.

CULTURE.—*Ps. pyocanea* was recovered from the liver. The addition of chloramphenicol inhibited its growth in the inoculated animals. Semi-confluent local lesions developed on the chorio-allantois of chick embryos after 48 hours' incubation. Morphologically these were very small and were similar to those produced by herpes simplex virus on primary isolation. Evidence of infection was also established both in newborn and in adult mice whereas no such signs developed in the rabbit or guinea-pig.

SEROLOGY.—Very little serum was obtained at necropsy and, as this was completely anticomplementary, antibody was estimated by the neutralization test using the plaque-counting method on the chorio-allantois (McNair Scott, 1948). For technical reasons it was not possible to test the child's serum in as much detail as had been hoped; neither was it possible to obtain serum for testing from the mother and child on the same day. It would, therefore be inadvisable to draw rigid conclusions from the results that were obtained.

In the case of the mother and several positive control sera (human) complete neutralization (i.e. 90%-100%) was obtained with the sera diluted 1 in 80. Known negative sera (acute phase samples from cases of primary herpes simplex) showed no neutralizing activity at 1 in 4. On the other hand, the serum from the child showed a 50% reduction in the plaque count at 1 in 4, from which it was concluded that antibody was present in low titre.

Herpes simplex virus was identified as the causative agent by the demonstration of intranuclear changes with inclusions in the infected tissues and by the inhibition of these changes with specific herpes antiserum.

Histology

The tongue, uvula and posterior pharyngeal wall showed similar changes although they varied in degree in different sites. The mucosa was everywhere intact but varied in thickness; in some areas it was thinned and oedematous and the nuclei were swollen and often bizarre; elsewhere it was hyperplastic and contained many mitotic figures together with some multinucleate cells. The sub-epithelial tissues were oedematous, contained prominent capillary vessels, and were infiltrated diffusely with many lymphocytes and some macrophages, polymorphs and eosinophils. The changes were non-specific and no inclusions were seen (Fig. 2).

In the upper oesophagus there were several sharply demarcated microscopic foci of recent coagulative

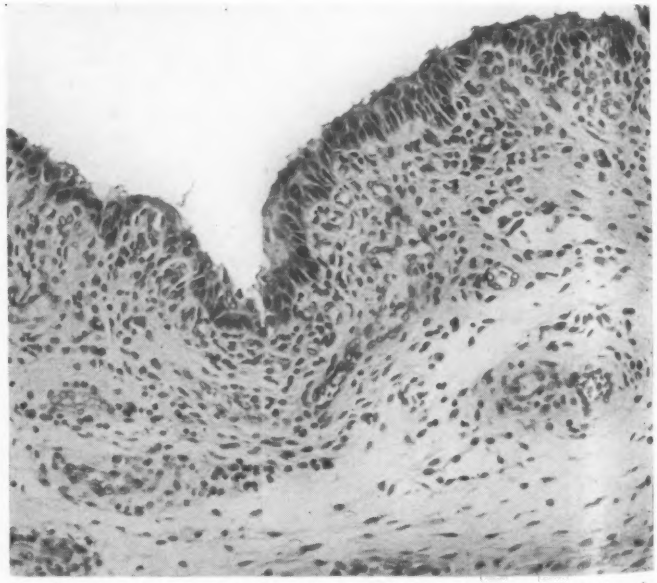

FIG. 2.—Posterior pharyngeal wall: the epithelium is ragged and the sub-epithelial tissues are well vascularized and contain chronic inflammatory cells. Haematoxylin and eosin × 140.

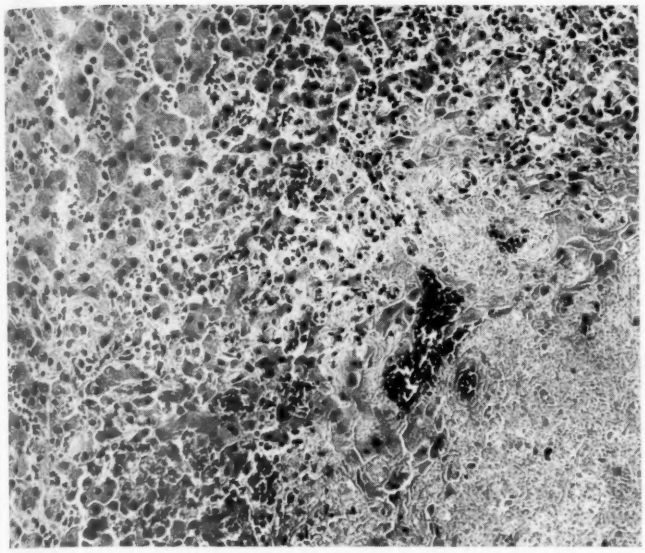

FIG. 3.—Liver: edge of a necrotic focus showing the clear line of demarcation between the necrotic and intact cells. No inflammatory cells are present in the necrotic tissue. Haematoxylin and eosin × 140.

necrosis of the mucosa which were separated by intact but oedematous epithelium. The submucosa contained some lymphocytes, polymorphs and eosinophils. The changes were non-specific and were almost certainly the result of tube feeding. The lower oesophagus was normal.

The liver parenchyma contained many sharply demarcated areas of coagulative necrosis scattered irregularly throughout both lobes, often in close relation to blood vessels (Fig. 3). They varied in size from minute areas involving a few cells to extensive zones affecting one or more lobules. Many of the smaller lesions were of recent origin and, although nuclear and cytoplasmic degenerative changes were marked, the general architecture of the lobules was preserved. The larger lesions were older and the liver cells had been transformed into a structureless, eosinophilic mass with some distortion of the reticulin framework of the lobules. None of the lesions showed any evidence of healing. Many of the larger foci contained numerous Gram-negative bacilli. A noticeable feature was the relative absence of inflammatory exudate in the lesions, although at the periphery of some of the foci the sinusoids frequently contained large numbers of red cells together with some lymphocytes and macrophages. Even more striking, however, was the presence of nuclear changes in the parenchymal cells at the margins of the necrotic areas. Many of the nuclei were swollen and contained large nucleoli but there was no obvious alteration in the arrangement of the nuclear chromatin; these changes are quite commonly seen in herpes but are not specific for that disease. Other nuclei were considerably swollen and showed the features that are characteristic of a relatively early stage in the development of a herpes inclusion; the chromatin was marginated and nodular, while the central part of the nucleus was occupied by a homogeneous, deeply basophilic inclusion. Many cells contained the eosinophilic inclusions which are typical of a later stage in development (Cowdry type A inclusions); the nuclei were enlarged, the inclusions lay centrally and were surrounded by a clear 'halo', from which the nuclear chromatin had disappeared, while the nuclear membrane was deeply basophilic, thickened, nodular and sometimes crenated (Fig. 4). An occasional cell was seen in which the inclusion had evolved still further as the nucleus was now somewhat smaller and the nuclear membrane had contracted down on the eosinophilic inclusion so that the clear halo had disappeared.

The diaphragm and omentum contained focal necrotic areas that were essentially similar to those seen in the liver.

The remaining viscera, and especially the adrenals, the lungs and central nervous system, were examined

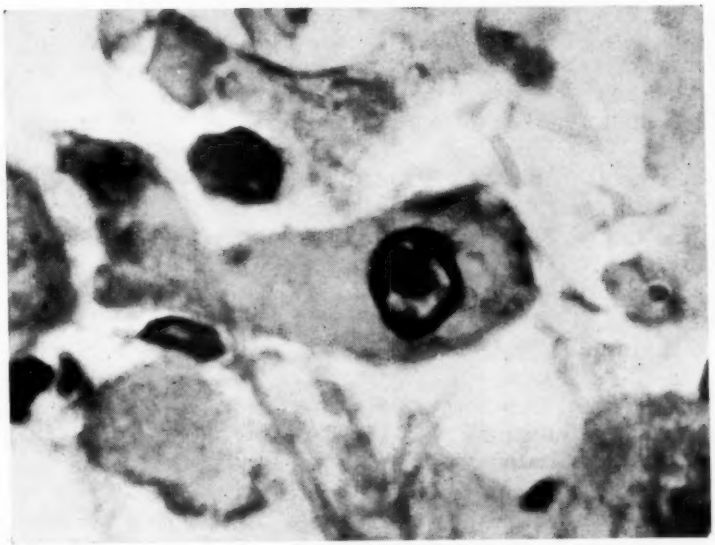

FIG. 4.—Liver: fully developed acidophilic intranuclear inclusion in a cell at the margin of a necrotic focus. Haematoxylin and eosin × 1,900.

for the presence of necrotic foci and intranuclear inclusions but no specific herpetic lesions were seen.

Section through one of the skin lesions showed that there was widespread necrosis of the dermis and subcutis, with partial and irregular necrosis of the epidermis. The necrotic tissues contained many Gram-negative bacilli but there was no inflammatory cellular reaction. In the absence of any specific nuclear changes, the most likely explanation is that these lesions were of pyaemic rather than viral origin.

The myocardium showed cloudy swelling and oedema. The presence of bronchopneumonia in the lungs was confirmed. The brain was congested and oedematous.

Discussion

At necropsy this child was found to have necrotic lesions in the liver and diaphragm; they were of distinctive appearance and were due to the local action of herpes simplex virus, which was recovered from the liver. There were healing inflammatory lesions in the oro-pharyngeal mucosa which could not be attributed definitely to the virus. Traumatic lesions, probably the result of repeated intubation, were seen in the upper oesophagus and there was also a terminal *Ps. pyocyanea* septicaemia with pyaemic skin lesions.

Visceral necrosis due to dissemination and focal multiplication of virus is a rare complication of certain virus diseases, such as vaccinia and varicella, but its occurrence in herpes simplex infection is only of recent recognition. Dissemination occurs by means of the blood stream, in much the same way as a pyaemia may occur in a bacterial infection, and like a pyaemia the extent of visceral involvement may vary from case to case although the liver, adrenals and lungs are particularly liable to contain metastatic viral lesions. A histological point that should be emphasized is that, apart from specific differences in the position of the inclusions within infected cells, the individual lesions in the viscera are strikingly similar in all three virus diseases. Also the microscopical appearances, especially the sharply outlined areas of parenchymal necrosis with minimal inflammatory reaction, are sufficiently characteristic to suggest that they are of viral origin.

In this case it has been shown that the liver lesions were produced by herpes virus and their presence can only be explained by blood stream spread from a focus of infection elsewhere in the body. There is no history of exposure to herpes virus nor is there unequivocal evidence as to the site of the primary lesion from which dissemination occurred. The skin 'spots' were transient and were not characteristic of herpes so that it seems likely that the portal of entry of virus was somewhere in the oro-pharynx. The clinical evidence does not exclude this and the histological changes are quite compatible with the healing phase of a primary herpetic lesion.

It is not known whether viraemia is a constant feature of herpes infections or whether it only occurs under certain abnormal circumstances, when it is responsible for the complications of the disease. More work needs to be done on this point but the fact that isolation of herpes virus from the blood stream has only been achieved on a few occasions indicates that the viraemia is almost certainly a transient one occurring early in the infection, as has been proved to be the case in the acute exanthems, such as smallpox (Downie, McCarthy and MacDonald, 1950; McCallum, McPherson and Johnstone, 1950).

When compared with the cases of disseminated herpes simplex reported by Zuelzer and Stulberg this case shows a number of interesting points of difference both in the course that the disease took and also in the extent of visceral involvement found at necropsy. Their two groups have already been referred to, Group 1 consisting of five newborn premature infants who died after a fulminating illness and had widespread visceral lesions due to herpes virus, and Group 2 comprising three older children with a gingivostomatitis and less extensive visceral involvement, largely confined to the liver. They attributed the different response to the virus in their two groups to the age at which infection occurred and suggested that the greater clinical severity and wider dissemination of virus in their Group 1 cases was due in part to the greater susceptibility of embryonic tissue. That age alone does not determine the clinical course and amount of visceral involvement is, we think, shown by the pattern of visceral lesions in our case, which resembles that of their Group 2 rather than their Group 1.

Although primary herpetic infection may occur at any age, the majority of individuals become infected during childhood, usually between the ages of 1 and 5 years (McNair Scott *et al.*, 1952). Infection early in infancy, particularly in the neonatal period is, to our knowledge, extremely uncommon. This is probably due, in part at least, to protection afforded by maternal antibody which normally persists in the infant's circulation for the first four to six months of life (Anderson and Hamilton, 1949). The mother of our case was found to have herpes antibody in high titre four months after the birth of her child, and it is safe to assume, considering her age and the absence of any history of primary infection, that antibody was present at the time of her confinement.

In which case, assuming that antibody passed across the placenta in the normal fashion, the child was infected whilst possessing maternal antibody. Similar serological findings were reported by Zuelzer and Stulberg (Case 1: Zuelzer and Stulberg, 1952).

Taking all factors into consideration it is difficult to offer an explanation of the finding of herpes antibody in such low titre in this infant as, under normal conditions, one would expect a close correlation between the antibody level in mother and child at the time of delivery. If we are in fact correct in our interpretation that antibody was present in low titre it would seem that this can be explained in one of two ways; either maternal antibody disappeared unduly rapidly or active immunity failed to develop *pari passu* with the infection. Unfortunately the serological investigations were too limited to allow any definite conclusions to be drawn on this point.

Summary

A fatal case of disseminated herpes simplex in a newborn infant is described. The oro-pharynx is suggested as the site of primary infection. Visceral lesions were confined to the liver and their herpetic aetiology was established by the pathological findings and isolation of virus. A marked difference was found in the serum antibody titre in mother and child.

We are grateful to Dr. Marjorie L. Pennill of the Mildmay Memorial Hospital, London, for details of the child's health during the first week of life. We are indebted to Dr. Martin Bodian for helpful criticism in the preparation of this paper and to Mr. Derek Martin for the illustrations.

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Addendum

Since this paper was written France and Wilmers have described herpes simplex hepatitis and encephalitis in newborn twins. (France, N. E. and Wilmers, M. J. (1953), *Lancet*, **1**, 1181.)

A CLINICAL STUDY OF THE DRAUGHT REFLEX IN HUMAN LACTATION

BY

CLAIR ISBISTER*

From the Unit of Clinical Investigation and the Department of Obstetrics, the Royal North Shore Hospital of Sydney, Australia

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The problems of human lactation have lost their urgency and unfortunately even their interest for the majority of the medical profession since the introduction of safe and satisfactory artificial foods. But for thousands of lactating women the problems are no less acute now than they were for their ancestors. The joy and sense of achievement given by satisfactory lactation is no less real nor is the sense of dissatisfaction and personal inefficiency less acute because of the existence of satisfactory substitutes.

History of the Draught Reflex

The idea that milk flowed and was not merely sucked out was quite familiar in ancient and medieval times. Some of the best clinical observations on human lactation are to be found in the works of Avicenna (see Duncum, 1947), the 'prince of physicians', in Baghdad in the eleventh century. No modern textbook has anything to add to his care of the lactating woman, and there is no better description of the woman who lactates well than in his writings on 'the selection of a wet nurse'. Avicenna, writing on the flow of milk, says:

> ' If there is anything to prevent the mother from giving milk to her babe, such as because it runs too quickly . . . a wet nurse should be selected', and again 'A little milk may be drawn from the breast before each feed to encourage and facilitate its flow.'

Another reference to the flow of milk may be found in the records of the Hospital of the Holy Ghost in Rome, where there is a sixteenth century fresco illustrating a group of wet nurses feeding foundling children to the soothing accompaniment of a musician playing the renaissance equivalent of the oboe, the purpose of this music being 'the beneficial influence of soft and melodious music on the flow of mothers' milk!' Rubens' famous 'War and Peace' and Tintoretto's 'Milky Way' in the National Gallery, London, also incidently illustrate milk ejection.

Much of this knowledge has been lost or forgotten. In 1947 I made some detailed observations on the occurrence of the draught, or 'let-down' reflex, in my own third lactation and found that there was very little reference to it in the current literature, except in the writings of Waller (1938, 1943, 1947a, 1947b). I discussed my findings with colleagues well versed in infant feeding and found that many had never heard of it. Those who had heard of it regarded it of little importance in the management of lactation and thought it occurred in only a few patients. My efforts to point out that it occurred very commonly resulted in the criticism that the highly suggestible, nervous puerperal woman will feel anything she is asked to, and I decided not to publish my observations without further confirmation. A year later a visit to the National Institute for Research in Dairying at Reading, England, made me familiar with the work of Folley (1947), Ely and Petersen, (1941) and Richardson (1947). Soon after this the first article of Newton and Newton (1948) confirmed my observations, and I decided to collect a series of patients in an effort to determine the normal pattern of the draught reflex, and, if possible, to observe its disturbances and whether they produced symptoms in the baby.

It is easy for most lactating women to observe that while the baby sucks at one breast, milk often flows from the other and a sensation of 'pins and needles' or 'drawing' occurs in the breasts. Ely and Petersen (1941) beautifully demonstrated the let-down reflex in dairy cattle as a reflex mechanism in which afferent nervous impulses from the teat are carried to the posterior pituitary gland. The oxytocic principle released probably causes contraction of myoepithelial cells surrounding the alveoli. Richardson (1947) stained these contractile cells in the goat. Since then the let-down reflex has been demonstrated in many species (Whittlestone, Bassett and

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Turner, 1952; Whittlestone and Turner, 1952; Cross, 1952; Cross and Harris, 1952; Braude and Mitchell, 1952; Petersen and Ludwick, 1942). Other physiologists have more clearly demonstrated the path of the nervous impulses (Andersson, 1951) and the hormonal factors (Selye, Collip and Thomson, 1934; Selye and McKeown, 1934a and b). In the human subject Waller (1950, 1952) has demonstrated that the draught homogenizes the milk, that it becomes effective earlier in multiparae than in primiparae, and that it appears to pass through three stages. Newton and Newton (1950, 1951) have demonstrated that it occurs more frequently in successful lactations and that it is inhibited by fear, pain, anger, embarrassment and by an injection of adrenalin. They have shown also that the reflex can be stimulated by an injection of posterior pituitary hormone (cf. Gunther and Stanier, 1949). Miller (1952) has associated failure of the draught with failure of lactation. However, little of this accumulating knowledge of the draught reflex has yet been applied to the actual problems of lactation.

Method of Investigation

The draught itself was investigated in four different ways: (*a*) Subjective sensation of the mother, (*b*) intermittent leaking or rapid flow observed by the mother, nurse or doctor, (*c*) by closely observing the sucking movements of the baby while feeding and (*d*) by the use of the breast pump or hand expression of the breasts.

Observations were recorded on four groups of women.

Group 1. Group 1 were primiparae passing consecutively through the wards of a maternity hospital. They received routine hospital care, were not told about the draught and were sent a written questionnaire after six months' lactation. They had no personal contact with me except by letter to ensure that I personally did not affect their answers.

Group 2. Group 2 were consecutive admissions to a mothercraft home, both multiparae and primiparae; these I watched personally and most were asked to note any sensations, but were not told that they would be followed up.

Groups 1 and 2 were examined in the puerperal period and followed up after six months by a written questionnaire and were requested to write if they felt that they had more information to contribute. One hundred and six did so, 20 in detail. The following information was requested:

MATERNAL. Sore or cracked nipples; overloaded breasts; mastitis or breast abscess; leaking breasts; fall in supply on returning home; too rapid flow; not enough or too much milk; housing and other worries.

BABY. Difficulty in sucking; fighting at the breast; wind; colic; frequent stools; vomiting; general condition and incidents at 3 and 6 months; weight at 3 and 6 months.

FEEDING. Duration; partial or entire at 3 and 6 months; reason for weaning.

DRAUGHT. (This is described as the 'tingling or drawing sensation of milk coming into the breast that some mothers feel during or between feeds'.) Occurrence; time in relation to feeds; duration; on one or both sides; when first felt; nature of sensation, e.g. strong, moderate.

Group 3. Group 3 was a small selected group of seven mothers (four primiparae and three multiparae) who were accurate observers and who kept detailed studies during the whole of lactation, observing relation of draught to feeds, timing, duration and factors influencing it. This included my own fourth lactation in 1951.

Group 4. Group 4 consisted of 33 interested mothers who kept records during the establishment of lactation. They were mainly selected from my paediatric clinic or the Carpenter Mothercraft Home and were representative of a wide social and intellectual field.

In addition, over a three-year period I closely observed breast feeding in a 60-bed maternity hospital, a 10-bed mothercraft home and a follow-up clinic where particular note of the draught reflex in normal and troubled lactations was made and observations by mothers were verified.

Observation of Draught

Subjective Sensation of the Mother. This is a very distinct feeling which she has no difficulty in recognizing once she has felt it, although from my own experience I could appreciate that it could become so much a part of one's everyday life as to be almost subconscious, unless especially observed. It is described in many ways: as 'pins and needles', 'tingling', 'drawing feeling', 'rushing down feeling' or a 'kind of pain' sometimes associated with slight nausea. Most mothers could note the time of onset in relation to feeds fairly accurately, as it starts sharply. Most had difficulty in estimating the duration of a sensation that gradually decreases in intensity. Associated symptoms may occur in the puerperium, e.g. after pains, bleeding per vaginam, and intestinal colic.

Evidence of Intermittent Leaking or Rapid Flow. When the draught occurs between feeds the milk may leak or gush from the nipples. Two patients who were test weighing after every feed made the spon-

taneous observation that if they had a shower before the baby's feed, milk poured from the breasts and the subsequent feed was 2 oz. less than usual. When the baby is put to one breast, milk may be seen flowing from the other but the loss does not seem to be as great as indicated above. This coincides with the subjective sensation of the mother and in some patients will resemble a fountain spurting.

Observation of Sucking Movements of the Baby. In established lactation, three stages of feeding can be seen: (1) The baby sucks or nibbles the nipple with only occasional swallows, often in a restless, hungry fashion for a period lasting a few seconds to a minute. (2) It then becomes quite still, sucking and swallowing in a regular rhythmic fashion with closed eyes and intense concentration for a period of one to three minutes. (3) It begins to move again, sucks in a more leisurely fashion or even stops and goes to sleep, until moved to the other side when it again sucks and swallows in a rhythmical fashion, but without the concentration of the first side. Similar observations have been made in rabbits (Cross and Harris, 1952). Close observation of the baby feeding during the establishment of lactation will often show whether the milk is 'down', whether it is flowing or is coming down intermittently.

Use of Electric Breast Pump or Manual Expression. This sometimes shows when the draught is occurring. Suction may be applied for 30 seconds or more before the milk flows from the first breast which can then be emptied in a few minutes. The other side can then be emptied without any wait as the milk is 'there'. If the draught has occurred before the feed the milk usually flows easily on suction and the breasts can be emptied in a few minutes.

In some patients one can observe periods when milk comes intermittently with intervals of no milk. It is essential that the patient should be used to the pump or the reflex may be inhibited.

There was no appreciable difference in the observation made on the draught reflex by Groups 1 and 2. Therefore the observations concerning the 241 mothers in Groups 1 and 2 will be analysed together.

Incidence of the Draught Reflex

Of the 241 patients in Groups 1 and 2 lactation had failed at three months in 38 and was still being carried on at six months by 160 (128 fully feeding). Of the 160, 137 stated that they felt the draught either during or before feeds on one or both sides (121 both sides, 12 on opposite breast when baby was sucking, four no record), 11 did not feel it and 12 did not complete this section of the form. Of the 11 (two partially feeding) who did not feel it, seven filled in 'rapid flow' or 'intermittent leaking', so indicating that they had observed it and four said they could 'see it flowing but could feel nothing'. Four of the 11 were from the same health centre and the form was filled in by the Sister. Unfortunately, though I had verbally explained what the draught was to the sisters, I had not given them the routine letter to mothers. The final results showed that most who left the section on draught blank were women followed through health centres where the Sister had not understood or where the patient's form had been filled in from records only. Mothers recognized what I was talking about with alacrity if they were breast feeding. Of the 38 who were artificially feeding at three months, 18 had not felt anything, 10 felt the draught, and 10 left the section blank.

The Physiological Pattern of the Draught Reflex

This cannot be reported with mathematical accuracy as so many patients from all four groups contributed observations which had not been anticipated in the questionnaire. My own detailed observations gave a clear picture confirmed by other multiparae. Only a composite picture appears of what happens to the primiparae, as variations seem considerable during the 'establishment of lactation', which may be defined as the period between the start of lactation and the maintenance period when a regular feeding pattern and stable daily output have been attained.

Multiparae. My own record during my fourth lactation was as follows. Occasional weak draughts were felt during the last two weeks of pregnancy when emotionally excited, also a few of feeble intensity were felt during labour. Twenty-four hours after delivery a weak draught sensation occurred with suckling and a stronger one 24 hours later. The breasts then filled and from then on draughts occurred with each feed and between feeds; they varied in intensity and were associated with severe after-pains, intestinal colic and bleeding per vaginam. After-pains became less after the fourth day but bleeding per vaginam still coincided with the draught up to the tenth day. For the first month, the draught was not regular; it sometimes came in 10 seconds after putting the baby to the breast, at other times in 30 seconds and sometimes while getting ready for a feed. It was easily elicited by stimulating the nipple, by thinking or talking of the baby and by taking fluids. It varied in intensity and sometimes occurred twice in a feed and between feeds. By the end of one month draughts occurred regularly 10 seconds after putting the baby to the breast and only occasionally twice during a feed or

between feeds. The baby was fully breast fed and lactation appeared to be established.

The observations of other multiparae confirmed these findings, except that most appeared to be getting the draught as they prepared for the feed and many were still getting the reflex between feeds at the end of one month.

Primiparae. Most primiparae felt no draughts until the third week of the puerperium or later, and in the case of one in Group 3 not until the eighth week when she was fully feeding for the first time. There happened to be a few in the series who had been instructed in Dr. Waller's technique of prenatal breast preparation and some of these felt the draught in the first week, like the multiparae. The primiparae observed that it was eight weeks before most of them were getting regular draughts, at feed time only, on sensory stimulation of the nipple either by the baby or by washing the nipples. Both multiparae and primiparae observed that during the establishment period the draught was easy to elicit in the following ways: (*a*) stimulation of the nipple, (*b*) psychological stimulation, e.g. hearing the baby cry, thinking of feed, (*c*) taking fluids, (*d*) full breasts, e.g., at night, (*e*) having shower or swim, i.e., hot, cold or tactile stimulation, (*f*) undoing brassiere, i.e., relief of pressure, (*g*) physical exertion, e.g., running, tennis, involving movement of the breasts.

Observations Common to Both Multiparae and Primiparae. Mothers had been asked to attempt to estimate the time between sensory stimulation and feeling the draught. The interval appeared to be regular for each individual at any particular period, from milk coming at once to 30 seconds, the majority being about 10 seconds. In my own record the reflex was quite regular at 10 seconds for two and a half months. This gradually lengthened to 20 seconds in the third month, 30 in the fourth and by seven months it was taking a full minute to elicit. Supply was failing, weaning was started, and the period lengthened to one and a half minutes when the draught gradually disappeared. I also observed that at the 10 p.m. feed the draught was much more difficult to elicit after the fourth month when, in contrast to other feeds, it was always a minute or longer; this was also noted in my previous lactation. In the previous lactation, at seven months the draught was coming in 45 seconds with a better milk supply.

Both multiparae and primiparae observed that it became less easy to elicit by the end of the first three months when it would only be elicited by sensory stimulation of the nipple. The experience of many mothers was that the draught became more difficult to elicit in the latter months and gradually disappeared at weaning. This was also a common observation in those whose lactation failed early. Two in Group 3 stated that the period remained regular from three months to weaning time then became more difficult to elicit; but the figures given are not sufficiently detailed after three months.

Mothers were also asked to note the duration of the draught. This proved very difficult because of the nature of the sensation which is a strong, sharp, at times almost painful, contraction which gradually decreases in intensity so that the time of disappearance cannot be noted. The results varied from 15 seconds to one and a half minutes and even after sensation ceased milk could still be seen flowing. Many patients noted that at times the draught was slower in coming and seemed to last a shorter time. This appeared to be associated with such factors as embarrassment, fatigue and worry, painful nipples and diminishing supply. I confirmed this on several occasions, e.g. anger aroused just before a feed delayed the draught to two minutes, by which time the baby was fighting and screaming. The questionnaire took housing as a possible factor influencing lactation and it was found that of the 137 who felt the draught and were feeding at six months, 35 had a housing problem (25%), but of the 28 artificially feeding at three months, 11 had a housing problem (39%).

Variations from Average

Multiple Draughts During a Feed. This occurs in the first two months and two to four draughts may occur during a feed. These were confirmed by watching the baby feed and checking on the pump. All occurred in the group with feeding troubles and were emotional patients helped by a sedative.

Absence of the Draught Sensation. Primiparae do not feel it for about three weeks but observations by other means confirm that it occurs frequently and irregularly. There appeared to be considerable variation in the sensitivity of different patients. Many felt it only on the opposite side to the side at which the baby was feeding, others at some feeds only, usually the early feeds. A small group of those fully feeding did not feel it at all; three of these and other similar patients were closely observed. Draughts occurred, but most of the patients had big breasts with more sub-cutaneous tissue than usual and all had some feeding difficulties though they had an adequate milk yield.

Variations in intensity appear to occur but until a method can be devised for measuring it that does not inhibit it psychologically and that allows for the probable existence of a sphincter round the nipple (Cathcart, Gairns and Garven, 1948), no comment

can be made except on subjective sensations and observed rapid flow.

Symptoms in the Baby Correlated with the Draught

Observations were made on my own clinic patients, the mothercraft home patients, and, retrospectively, on Groups 1 and 2. I also occasionally noted symptoms in my own babies.

When the draught occurs after the baby goes to the breast and milk pours into the child's mouth, it may react in the following ways: (*a*) Drink as quickly as possible until the initial gush passes off, without developing any symptoms; (*b*) gulp, choke and withdraw from the breast, going back when the initial gush is over to finish the feed without developing symptoms; (*c*) fight and push away the breast and often refuse to go back; (*d*) gulp as fast as possible swallowing air and milk, and be unable to coordinate sucking, swallowing and breathing in the usual rhythmical manner. This may result in the baby getting such a full stomach that it subsequently vomits the feed or suffers from wind, colic and frequent stools. Some babies were observed to develop a gulping habit so that even after feeds were regulated they still tended to gulp and get wind.

Groups *b* and *c* were relieved by 'bringing in the milk' before putting the baby to the breast, i.e., evoking the draught by manual stimulation of the nipple and waiting until the subjective sensation of the draught was diminishing. Group *d* were also helped by 'bringing in the milk' at the beginning of the feed for a few days or weeks and by sedation of mother and baby. 'Posture feeding' (the mother lying on her back with the baby prone across the chest), which does not make the flow any slower but puts the baby in a better position to manage it, also helped. In most cases there was considerable relief of symptoms.

Where the mother felt multiple draughts, or where it could be demonstrated that the milk was coming down intermittently, the baby swallowed air and had colic.

Where the draught was inhibited and late in coming, the baby tended to fight the breast. I observed on many occasions that after one minute of ineffectual sucking my own baby would start to fight. In the retrospective study, five women stated that fighting the breast was the only trouble they had with breast feeding and this occurred at 5 months in four cases. Several mothers observed that the baby started to fight 'when the milk wouldn't come'. In a few cases fighting was observed with other symptoms in the early weeks, and was associated with cracked nipples and pain inhibiting the draught.

It appears to be worth reporting the following figures from the retrospective study. Underfeeding is almost eliminated as a cause of symptoms in the first three months. Of the 159 babies with satisfactory records, still breast fed at 6 months, 131 were first babies. Eighty babies with either gastro-intestinal symptoms or fighting the breast had mothers who felt the draught, and of these 48 mothers described the draught as strong. Of the 64 babies with no symptoms, whose mothers felt the draught, 25 mothers described the draught as strong.

There appears to be a correlation between strength of the subjective sensation of the draught and leaking breasts, rapid flow and a high yield. The babies, with only one exception, had gastro-intestinal symptoms where strong draught was associated with these three observations though the numbers are too small to make firm conclusions. Also the highest incidence of no symptoms occurred in the 'moderate draught' group who were not troubled by leaking breasts, rapid flow or too much milk.

Discussion

Occurrence of the draught reflex in at least 137 of the 148 patients breast feeding after six months whose records were complete (97%) proves that effective reflex expulsion of milk is essential to successful lactation. This is supported by the high percentage who did not feel it and had resorted to artificial feeding by three months.

The Physiological Pattern. It seems fairly clear that the draught reflex occurs as a contraction of myoepithelial cells surrounding the alveoli from the time milk appears in the breast, i.e., about the third day. These contractions can be felt by multiparae in the first week but not usually by primiparae until about three weeks after delivery or later. During the period of establishment of lactation the draughts occur at feed times, either just before or during feeds, and usually once or twice between feeds. They are easily elicited by a number of factors. The period of establishment appears to be one month or less in multiparae and two months or more in primiparae. The reflex then occurs regularly at feeding times, usually only once, and is elicited by sensory stimulation of the nipple. The reflex gradually becomes more difficult to elicit until weaning time (seven to eight months) when it gradually disappears.

Variations in this pattern, particularly in time, occur but the observations and numbers used were not sufficient to give a final picture. The observations on my own lactation were detailed, but they may, however, have been affected by the need of a complementary feed once daily after three months.

Symptoms in the Baby Related to the Draught. It appears that two main syndromes may be associated with the strength and timing of the draught reflex. (1) Fighting the breast in response to (*a*) a gush of milk that is difficult for the baby to manage. This occurs in the first two months. (*b*) A delay of more than one minute in the draught so that there is no milk in response to suckling and the baby becomes impatient. This occurs later, at about 5 months when the draught is less easy to elicit. (2) Gastro-intestinal symptoms, e.g. vomiting, wind, colic, frequent stools which appear to be due to gulping large quantities of milk and swallowing air associated with incoordination of breathing and swallowing.

It is worthy of note that when the latter syndrome is attributed to 'overfeeding' the mother is often advised to curtail feeds instead of to regulate the flow with the result that lactation gradually fails from incomplete emptying of the breasts. This may be the reason that the syndrome is now more often attributed to underfeeding (Wickes, 1952). It is also tempting to correlate the 'three months colic' with the period of establishment of lactation and the irregularity of the draught.

However, these conclusions are only tentative and are presented as a preliminary report. It is necessary to plan a study in which multiparae are observed during the establishment of lactation, recording milk production, leaking breasts, milk pressures, particularly ejection pressures and symptoms in the baby. The high incidence of symptoms and the difficulty in assessing the importance of mothers' observations was largely due to the high incidence of primiparae in the series.

Practical Application and Conclusion. Careful observation of the baby at the breast will not only enable the doctor or health centre sister to observe faults in technique, but also to note the flow of milk and when it occurs. It is important for health centre sisters to be familiar with the draught reflex and its variations, especially in primiparae, and particularly with the fact that the unfamiliar surroundings and the anxious circumstances of a single test feed done in a clinic may inhibit the draught giving a false idea of yield. The simple trick of 'bringing in the milk' first when it tended to pour over the baby has helped to relieve colic in many infants. The practice of washing the nipples before feeding often achieves this, and gently rubbing or handling the nipple will bring down the milk. Actual expression is not necessary unless the baby has developed the gulping habit. It also appears that the practice of the mother of taking fluids before feeding her baby assists the 'let down' by conditioning the reflex. It is not suggested in any way that there are not other causes of swallowing wind, colic and fighting the breast, and no comments made here should detract from the importance of correct technique, position and adequate supply. Despite the insufficient numbers and the incomplete nature of this investigation it was felt that the results should be published as a preliminary to attempting a more detailed investigation, with the help of a physicist and a veterinary physiologist if possible.

Summary

An attempt is made to assess the place of the draught reflex in human lactation.

It is concluded that the presence of the draught reflex is essential to successful lactation and that over 95% of patients with established lactation are conscious of the subjective sensation of the draught.

An attempt has been made to describe the pattern of the draught reflex during lactation and some variations are described.

A syndrome in the baby is described that appears to be due to a copious flow of milk associated with a strong draught reflex, i.e., ejected at high pressure. The symptoms are wind, colic, vomiting, frequent stools and sometimes fighting at the breast in the first three months. It is noted that these symptoms are often attributed to overfeeding. Fighting at the breast can also occur as a result of delay in ejection of milk.

The practical application is mentioned and the importance of observing the baby during feeding is stressed.

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PETECHIAE WITH CYANOSIS IN THE NEWBORN

BY

N. C. ELPHINSTONE, M. BRENDA MORRIS and SIMON YUDKIN
From Whittington Hospital, London

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In the past two or three years our attention has been drawn to a condition in newborn babies which, although not particularly uncommon, does not seem to be widely known and which may give rise to needless anxiety.

The doctor is usually called to see a baby which is born spontaneously but after birth appears to be grossly cyanosed. A nurse has usually put the baby into an oxygen tent. On two or three occasions a general practitioner who has delivered the baby or has been called in by the midwife has brought the baby to the hospital as an emergency.

When examined the baby is well and lusty. Most of the body is pink but the face and the head and part of the neck are dark purple. This colour sometimes also involves the lips and tongue. On looking more closely at the skin of the face there is seen to be a multitude of almost confluent petechiae but the cyanosis extends to the lips and tongue where there are no petechiae and sometimes a little beyond the edge of the petechial area. Occasionally there is also a sub-conjunctival haemorrhage.

The petechiae change colour during the next few days and have usually gone by the tenth day. The accompanying cyanosis lasts only for a day or two. The rest of the clinical examination is usually completely normal.

Sometimes, but not more frequently than in other babies, the hands and feet of these babies show 'peripheral' i.e., local, cyanosis with poor circulation.

No treatment is necessary.

These babies prompted us to look more carefully at the incidence of petechiae on the skin of the newborn and a series of babies was examined. It soon became obvious that many petechiae were missed unless very carefully looked for. A series of 98 babies was therefore examined with great care within a few hours of birth in bright daylight; a glass slide was used to differentiate between minute blood vessels and petechial haemorrhages.

Petechiae were searched for on the scalp and face and on the rest of the body.

In about a quarter of the babies presenting by the vertex there were petechiae limited to a small area of the scalp only, but in about a further half of the babies there were petechiae elsewhere in addition, usually on the forehead, cheeks, chin or neck. Only very occasionally were they found in other parts of the body and then they were much less numerous than on the face and neck.

In babies born by breech delivery the petechiae if present were on the presenting buttock.

In this series there were five babies born by Caesarean section. In none of these had the head engaged in the pelvis. Four had no petechiae and one had a single petechial haemorrhage on the scalp.

Since this series of babies was examined a baby, who was born by Caesarean section, has been seen with gross local cyanosis and petechiae involving the face and to a lesser degree the scalp and neck. This baby's head was delivered with difficulty with the aid of forceps and was held in the uterine incision, with the face presenting for some 30 to 60 seconds.

In only 34 of the babies were no petechiae found.

An attempt was made to see whether subconjunctival haemorrhages were correlated with the degree of petechiae. Of 74 babies whose eyes were examined, 10 had subconjunctival haemorrhages and in eight of these there were petechiae elsewhere than on the scalp.

Analysis of various factors showed no correlation between the incidence of petechiae and maternal history, the type of delivery, length of labour, anaesthetic and the condition of the baby at birth. However, they were more common in male than in female babies and tended to be more extensive in the heavier babies.

Prothrombin time and platelet counts were normal. One baby had petechiae sparsely distributed over the whole of the body, accompanied by a platelet count of 15,000/c.mm. The mother also had thrombocytopenia and this was considered to be a case of thrombocytopenic purpura of the newborn.

This condition of petechiae with accompanying

cyanosis seems to us to resemble traumatic cyanosis in older children and adults and it may be produced by an analogous mechanism.

Conclusions and Summary

Petechiae on the neck and head of the newborn baby (born by the vertex) are not uncommon, especially in large babies, and some petechiae were found in almost two-thirds of the babies examined.

When profuse they are usually accompanied by local cyanosis, an appearance which may cause needless anxiety. However, the baby is otherwise well and there is no central cyanosis.

Petechiae elsewhere on the body are rare in this condition and usually only sparse.

In babies born by the breech a similar condition occurs on the buttocks.

The condition seems to resemble traumatic cyanosis and may be produced by a similar mechanism, occurring during delivery of the presenting part.

We would like to thank Dr. Simpson, of the Pathology Department, for carrying out the haematological tests and the nursing staff of the Maternity Department who were so prompt in drawing our attention to the condition once it had been recognized.

THROMBOCYTOPENIC PURPURA IN THE NEWBORN

BY

M. BRENDA MORRIS

From Whittington Hospital, London

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Thrombocytopenic purpura in the newborn is an uncommon condition which has, however, been well reported. The literature has been reviewed by Robson and Walker (1951) who found 60 cases and added three of their own. These included 11 in which no platelet count was reported, but in which they considered that other evidence was adequate for their inclusion in the series, and two (Guttfreund, 1933; Lightwood, 1931) in which the condition did not present until four months and five weeks after birth respectively.

They classified these 63 cases as follows:

THROMBOCYTOPENIA IN 63 INFANTS

Group I ..	Infants born of mothers with thrombocytopenia purpura (*a*) Idiopathic (essential) including mothers who had had splenectomy. (*b*) Secondary to drugs, toxins etc., or from cause unknown.
Group II ..	Infants born of normal mothers

Twenty-seven cases have since been described (Åkerrén and Reinand, 1950; Boyette, 1951; Dobbs, 1950; Epstein, Lozner, Cobbey and Davidson, 1950; Gruber, Redner and Kogut 1951; Hauser, 1948; LaDriere, 1951; Litchfield, Sternberg and Zweifler, 1950; Randak and Danforth, 1951; Saltzman, 1949; Shipton, 1950 a and b; Weill and Grappe, 1951) all of which fall into one of these groups. It is of interest that six of these had thrombocytopenia (platelets less than 100,000/c.mm.) with no haemorrhagic manifestations.

Three further examples of this condition are reported one of which shows features in the mother which have not been previously described.

Case Reports

Platelet counts were performed by the indirect method of Dacie (1950).

Case 1.—Baby K., the first, a boy, was born at full term by forceps delivery. He had blue asphyxia at birth. Lobeline and 'synkavit' were given three hours after birth. Numerous petechial haemorrhages and ecchymoses which progressed, were noted. The spleen was not palpable. The infant vomited fresh blood and oozing continued from the injection sites. Six hours after birth biparietal cephalhaematomata began to appear and the cry became whining. The fontanelle was flat.

Haemoglobin was 105%, and practically no platelets were seen on a film.

Seven to ten hours after birth the infant had haematemesis and melaena and at 10 hours a transfusion of 90 ml. stored blood was given via the umbilical vein. At the end of the transfusion the fontanelle was noted to be full.

Twenty-hours after birth the infant was lying in the position of opisthotonus, but was not rigid. The fontanelle was full. A little melaena was seen but there were no other haemorrhagic manifestations after transfusion.

On lumbar puncture, 10 ml. of heavily bloodstained cerebrospinal fluid under increased pressure was withdrawn.

Haemoglobin was 150%, and platelets 18,000/c.mm.

On the sixth day the platelets had risen to 27,000/c.mm. and on the fifteenth day to 280,000/c.mm.

The baby made a gradual but satisfactory recovery and on the tenth day was behaving normally. He was discharged on the eighteenth day, breast fed and complemented.

At 3 months of age he was a normal baby, and a blood film showed normal platelets.

Baby K's. mother was aged 26, perfectly normal, and had had an uneventful pregnancy. Her platelet count on the second day after delivery was 300,000/c.mm., and on the fourth day after delivery, 240,000/c.mm.

Case 2.—Baby H., a third baby and a girl, was born at full term by normal delivery (birth weight, 6 lb. 6 oz.). A generalized petechial eruption developed over the trunk two hours after delivery. The spleen was not felt. The baby remained well and no other haemorrhagic manifestations occurred. She was breast fed.

On the first day platelets were 20,000/c.mm., and on the tenth day, 16,000/c.mm.

On the twenty-fourth day her platelets were less than 5,000/c.mm., on the thirty-fifth day less than 40,000/c.mm., and in the twelfth week, 120,000/c.mm.

The mother of Baby H. was aged 22. Her pregnancy and puerperium were uneventful. After the delivery of this baby it became known that she had had a splenectomy for chronic idiopathic thrombocytopenic purpura at the age of 14. She had had many haemorrhagic episodes between the ages of 9 and 14 years and had severe

menorrhagia from the time of the menarche. Her platelet counts before operation were about 20,000/c.mm. Since splenectomy she has been quite free of purpura and her menses have been normal. Unfortunately her platelet counts between splenectomy and this delivery are not available.

Her first child, a boy, aged 5 years, was circumcised at age 36 hours and required blood transfusion. No further information is available. He has been normal since.

The second child, a girl aged 3 years is normal.

The mother's platelets on the day of delivery were 150,000/c.mm.; on the fifth day after delivery, 700,000/c.mm.; on the fourteenth day after delivery, 60,000/c.mm., on the twenty-fourth day after delivery, 120,000/c.mm.; on the forty-first day after delivery, 215,000/c.mm.

Case 3.—Baby M., a second baby, a girl, was born at full term after a normal delivery (birth weight 6 lb. 14 oz.). A generalized petechial rash was noticed one hour after birth. The spleen was not felt. The baby remained well and no other haemorrhagic manifestations occurred. She was breast fed.

On the first day platelets were 15,000/c.mm. and on the fourteenth day, 50,000/c.mm. At follow-up in the fifth week the platelets were 140,000/c.mm.

The mother of Baby M. was aged 18, a Cypriot, in England for one year. Her past history was normal in all respects, and her pregnancy and puerperium uneventful.

Her first child, a girl, aged 14 months, was born in Cyprus, and the mother thought that the child had a petechial rash at birth. At 14 months this child's platelets were 240,000/c.mm., and she was physically normal.

The mother's blood count on the day of delivery gave: platelets, 50,000/c.mm.; Hb, 104%, red cells 5 m. per c.mm., leucocytes 10,400/c.mm. On physical examination nothing abnormal was found. On the fifth day after delivery platelets were 160,000/c.mm., on the fourteenth day after delivery 200,000/c.mm., and five weeks after delivery 226,000/c.mm.

Symptomless thrombocytopenia associated with delivery, as in the mother of Case 3, has not been previously reported. The platelet count had returned to normal by the eighth day and remained so five weeks after delivery. There was no history of any haemorrhagic manifestation in the past, of administration of drugs, or of any illness which might have caused thrombocytopenia.

There is little information available on the normal platelet counts during pregnancy and after delivery and this information is conflicting (Whitby and Britton, 1950; Shipton, 1950a) although changes in the platelet counts in relation to the menstrual cycle are known to occur (Goldburg and Gouley, 1940; Minot, 1936; Pohle, 1939).

Discussion

There have now been 80 infants reported in whom platelet counts are available; of these 63 have recovered, presumably completely, although in many of the earlier reports, summarized by Robson and Walker (1951), follow-up has not been extensive and serial platelet counts have not been recorded. Of the 30 cases recently described, 26 recovered. Twenty-four of these had serial platelet counts. Fourteen were followed for over one month, six for over three months, one for a year, and one for two years. All remained normal.

Splenectomy has been performed on two infants, one at 14 hours after birth (Gruber, Redner and Kobut, 1951) and one at 9 days of age (Bluestone and Maslow, 1949). Both platelet counts returned to normal but the first infant died at 30 days of intercurrent infection and there was no long-term follow-up on the second.

Seventeen of the 80 infants died. Eleven died from haemorrhage; nine within eight days of birth, one at four weeks and one (Hauser, 1948) at nine months of age. The remaining six died from other causes, one (Landolt, 1948) when the platelet count had already returned to normal.

Thrombocytopenia in the newborn resolves spontaneously, usually in one to three weeks, although it occasionally lasts several months. Fatal haemorrhage, uncontrolled by blood transfusion, may occur while the platelet count is low. The only case in which the condition has continued for longer than four and a half months is that described by Hauser (1948) in which the infant died of haemorrhage at 9 months of age. This case was complicated by severe sepsis and leucopenia which may have had some bearing on the outcome. The mother had thrombocytopenic purpura, probably of the chronic idiopathic type. The infant's platelet count was 100,600/c.mm. on the eighth day, but symptoms did not appear until the age of 6 weeks. From then until death he had recurrent haemorrhage, with finally no platelets in the peripheral blood. Repeated blood transfusions were of no avail. This is the only infant reported in whom the illness has pursued a prolonged course which might suggest the chronic type of idiopathic thrombocytopenic purpura described by Stefanini and Dameshek (1953).

Conclusion

It appears that, with possible very rare exceptions, thrombocytopenia in the newborn infant, irrespective of the state of the mother, is a self-limiting condition. In the majority complete recovery may be expected. There is a mortality of about 14% from haemorrhage while the platelet count is low.

Thrombocytopenic purpura of the newborn, although it may be due to the passage of some thrombocytopenia-inducing agent from the maternal to the foetal circulation (Epstein *et al.* 1950), does not progress to the chronic type of idiopathic thrombocytopenic purpura which occurs in children and young adults. Conversely it appears from the

fact that thrombocytopenia in the newborn recovers that chronic idiopathic thrombocytopenic purpura is not congenital.

Summary

Three further cases of thrombocytopenic purpura in the newborn are described.

In one of these the mother had a symptomless thrombocytopenia which was discovered on the day after delivery and which lasted less than a week.

The literature has been briefly reviewed and it is concluded that thrombocytopenia of the newborn is a self-limiting condition distinct from chronic idiopathic thrombocytopenic purpura.

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CHRONIC MYELOID LEUKAEMIA IN A CHILD PRESENTING AS ACUTE POLYARTHRITIS

BY

G. A. BEDWELL and A. M. DAWSON

From Charing Cross Hospital, London

(RECEIVED FOR PUBLICATION AUGUST 26, 1953)

It is well known that recurrent polyarthritis may occur in leukaemia of childhood, either as a presenting feature or during the course of the disease. The clinical picture, which often suggests rheumatic fever, has frequently been reported (Aisner and Hoxie, 1948; Baldridge and Awe, 1930; Poynton and Lightwood, 1932) and well reviewed by Dresner (1950). Many of these cases were of acute or subacute lymphatic leukaemia with an aleukaemic blood picture and only a few were of the myeloid type. It is rare in adults and little has been written about the pathological changes in the joints involved.

The following case is therefore thought worthy of record in that recurrent polyarthritis was the presenting feature in a child with chronic myeloid leukaemia which subsequently entered the terminal acute phase of the disease. Necropsy revealed leukaemic infiltration of the synovia of the two joints examined histologically.

Case History

In June, 1952, an 8-year-old schoolgirl developed joint pains and pyrexia and was admitted to another hospital two days after the symptoms started. Her mother stated that the abdomen had been swollen for one year but otherwise the child had been in good health.

Clinical examination showed a thin, pale child with a temperature of 103° F. and a pulse rate of 132 per minute. There was one enlarged lymph node in the left axilla. The spleen was grossly enlarged and extended into the pelvis. The liver was palpable two fingerbreadths below the costal margin. The skin over both knee joints and the right ankle joint was hot, while the left ankle joint was hot, red and swollen; movements of these joints were limited by pain. There were no other abnormal clinical findings. The blood picture was that of chronic myeloid leukaemia. A clinical diagnosis of chronic myeloid leukaemia and acute rheumatic fever was made. She was treated with aspirin, 15 grains four-hourly, and within 24 hours the temperature had settled and the joint condition subsided. Two days after admission she developed signs of splenic infarction with abdominal pain, tenderness over the spleen and a splenic friction rub. Some days later she developed a transient pericardial friction rub.

On July 1, 1952, she was admitted to Charing Cross Hospital. Clinical examination and laboratory findings confirmed the diagnosis of chronic myeloid leukaemia but there were no overt joint changes.

Special investigations showed; haemoglobin 57% (8·4 g.%), leucocytes, 133,200 per c.mm. (myeloblasts 0·5%, premyelocytes 7·5%, myelocytes 16·0%, metamyelocytes 15·0%, polymorphs 50·0%, eosinophils 3·0%, basophils 3·5%, lymphocytes 4·5%). The antistreptolysin titre was normal. No β-haemolytic streptococci were grown on a throat swab. The serum uric acid was 2·4 mg. %. A radiograph of the long bones and pelvis revealed no evidence of leukaemic changes on two occasions.

Five doses of deep x rays to the splenic region were given and resulted in a slight diminution in the size of the spleen and a reduction in the total white cell count. This showed on July 31, haemoglobin 42% (6·2 g. %), white cells 33,900 (premyelocytes 2·0%, myelocytes 23·5%, metamyelocytes 6·0%, polymorphs 63·0%, eosinophils 1·5%, basophils 1·0%, lymphocytes 3·0%), and platelets 188,800. She was transfused with five pints of blood after which the haemoglobin rose to 109% (16·2 g. %).

During the four months following admission she developed repeated attacks of pyrexia and joint pain affecting the fingers, wrists, elbows, shoulders, knees and ankles, at times accompanied by redness and warmth of the overlying skin with visible swelling of the joints. These attacks were sometimes accompanied by effusion into the joints with temporary periarticular thickening lasting 24 hours to 10 days. Finally the small joints of the left hand and both knees showed permanent periarticular thickening. Movements were always painful and much restricted during the acute phases. The attacks of febrile arthritis were not influenced by continual salicylate therapy of 90 grains daily (body weight, 52 lb.) while in Charing Cross Hospital. During the last six weeks of the illness her condition progressively worsened with irregular fever, emaciation, increasing anaemia and purpura; the superficial lymph nodes became enlarged and there was persistent localized pain and tenderness over the lower end of the left femur. The terminal white cell count showed 154,000 leucocytes per c.mm. of which 54% were myeloblasts. She died on November 2, 1952.

Necropsy.—The essential features were anaemia of all organs with widespread petechial haemorrhages into the

skin, pleura, pericardium and urinary bladder. All lymph nodes, both superficial and in the thorax and abdomen, were obviously enlarged. The spleen was grossly enlarged and weighed 1,090 g. and the liver was also enlarged but there was no macroscopical evidence of leukaemic infiltration. There were scattered leukaemic deposits in the vertebral, sternal and femoral bone marrow; the periosteum of the left femur was thickened due to leukaemic infiltration. The synovial membranes of the left knee and right elbow joints were oedematous and covered with scattered petechial haemorrhages, and histology showed extensive infiltration with leukaemic cells (Figs. 1 and 2). There was no microscopic evidence of rheumatic heart disease.

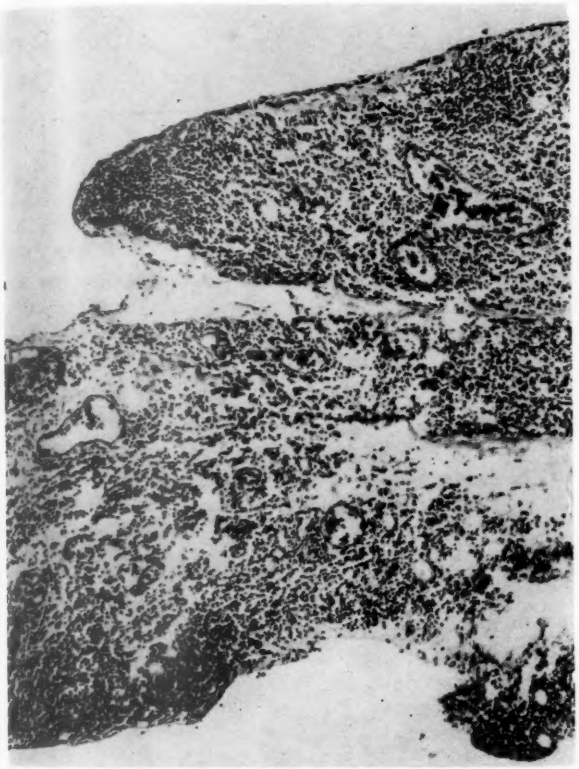

FIG. 1.—Synovial membrane infiltrated with immature white cells Haematoxylin and eosin × 70.

Discussion

The history of apparent good health with swelling of the abdomen for one year, the gross enlargement of the spleen and the original blood films all supported the diagnosis of chronic myeloid leukaemia. These findings were so typical that marrow examination was considered unjustified. The associated clinical diagnosis of acute rheumatism as suggested by flitting polyarthritis and pericarditis was not substantiated by the subsequent progress of the disease, the response to salicylates, the laboratory findings and finally by the necropsy.

Histological reports of the joints involved in leukaemia are, as stressed by Dresner (1950), remarkably scarce. He reported one case of leukaemic infiltration of the synovium and suggested that this was responsible for the joint manifestations in this disease. However, others have found no evidence of pathology in the affected joints and have attributed symptoms to nearby bony changes (Poynton and Lightwood, 1942; Bichel, 1948). Our case supports the view that leukaemic infiltration of the synovium of the joint can be responsible for the manifestations that occur in leukaemia, as both joints examined histologically showed this change. The persistent pain over the lower end of the femur apparently resulted from leukaemic infiltration of the periosteum.

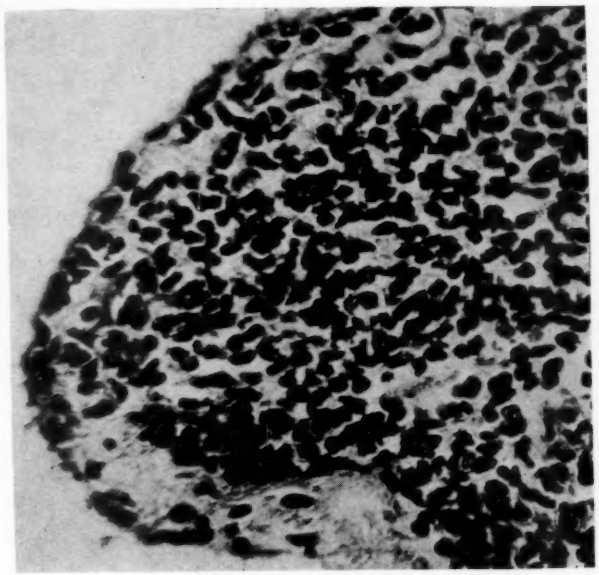

FIG. 2.—Inset of Fig. 1 × 500.

Summary

A case of chronic myeloid leukaemia in a child, which presented as acute polyarthritis is described. Histology showed leukaemic infiltration of the synovia of the two joints examined.

We would like to thank Dr. E. C. Warner for his permission to report this case and Dr. J. H. Shore for the post-mortem findings.

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ANNULAR PANCREAS IN THE NEWBORN

BY

P. P. RICKHAM

From Alder Hey Children's Hospital, Liverpool

(RECEIVED FOR PUBLICATION AUGUST 26, 1953)

In annular pancreas a collar or ring of tissue surrounds the second part of the duodenum. It is a rare malformation. Vidal published the first case in 1905; his patient was a newborn baby. In a recent publication, Swynnerton and Tanner (1953) collected 76 cases and we have found one more in the literature (MacPhee, 1953). In 1933 McNaught could only find 40 instances of this condition in the literature, most of them necropsy findings, but during the last three years over 20 cases have been published, all of them discovered at operation.

As annular pancreas is a congenital malformation, it is surprising that only nine of the 77 recorded cases were found in newborn babies. It therefore seems worth recording that we have encountered five neonates with this malformation during the last 18 months. It is likely that in the past many of the babies with annular pancreas giving rise to obstructive symptoms have died unoperated upon and undiagnosed. With the rapid advance of neonatal surgery, it is safe to predict that many more will be discovered and treated in the future.

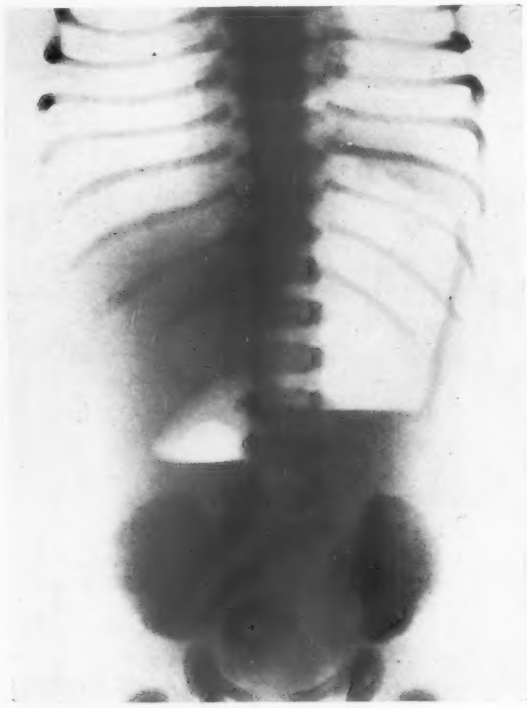

FIG. 1.—Case 1: radiograph of abdomen (patient sitting up). There are large air bubbles in the stomach and first part of the duodenum, but no air in the rest of the intestine.

Case Reports

The following are reports of three cases presenting with duodenal obstruction during the first few days of life:

Case 1.—Stephen was admitted on November 3, 1951, aged 2 days. He had been deeply cyanosed since birth and had vomited bile-stained material.

On examination, in addition to cyanosis, there was gaseous distension of the epigastric region and visible gastric peristalsis. An x-ray film confirmed the diagnosis of duodenal obstruction (Fig. 1).

At operation the second part of the duodenum was found to be tightly constricted by a ring of pancreatic tissue. A duodenojejunostomy was performed.

Recovery was uneventful. The cyanosis persisted and was later found to be due to tricuspid atresia. Mr. Ronald Edwards performed a thoracotomy when the boy was 12 months old, but decided not to undertake corrective measures. In spite of severe cyanosis, the child continues in good health (Fig. 2).

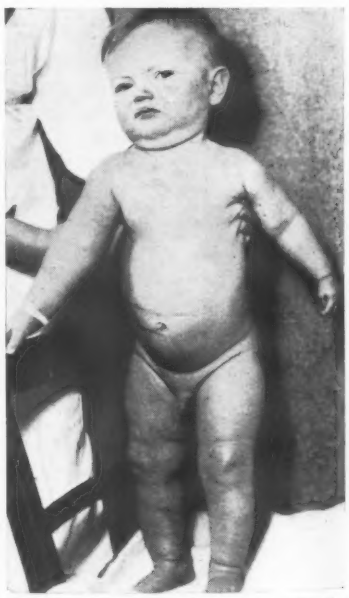

FIG. 2.—Case 1: the patient 18 months after operation.

Case 2.—Ronald was admitted on November 17, 1952, when 7 days old. He was a premature baby weighing

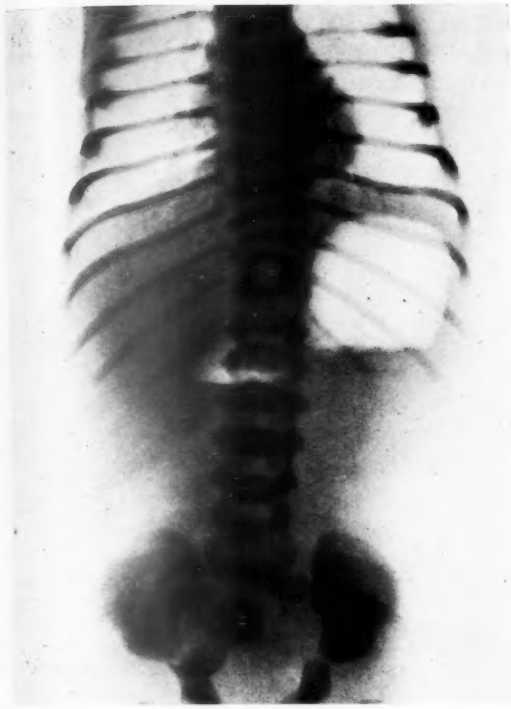

FIG. 3.—Case 2: radiograph of the abdomen (patient sitting up). The appearance is similar to Fig. 1.

2½ lb. He had vomited bile-stained material for four days.

On examination he was severely dehydrated and had signs of bilateral pneumonia. A diagnosis of duodenal obstruction was made on the x-ray films (Fig. 3). Intravenous infusion and gastric suction were instituted for 24 hours before operation.

At operation, there was gross dilatation of the proximal duodenum. Owing to the child's precarious condition, no attempt was made to dissect out the duodenum, which was considered to be atresic. A duodeno-jejunostomy was performed.

The baby appeared to be fairly well post-operatively but died a week later of pneumonia and prematurity.

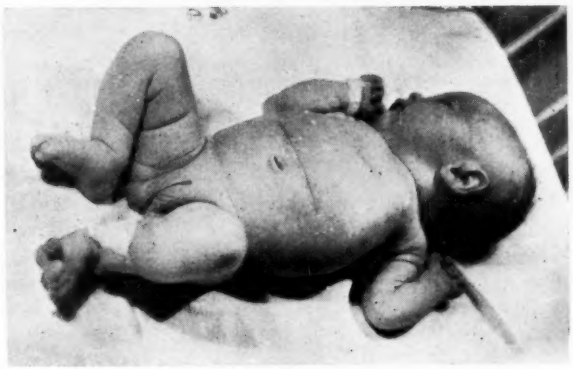

FIG. 5.—Case 3: the patient two months after operation.

Necropsy showed, in addition to bilateral pneumonia, a short segment of duodenal atresia at the level of the ampulla of Vater. The duodenum was surrounded by a ring of pancreatic tissue.

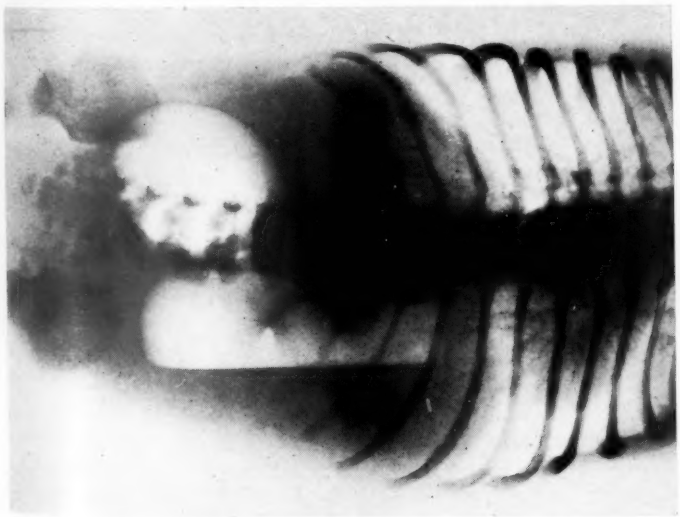

FIG. 4.—Case 3: radiograph of the abdomen (patient lying on the left side). The stomach and first part of the duodenum are outlined by air. There is no air in the rest of the small intestine.

Case 3.—Betty was admitted on January 10, 1953, aged 3 days, with a history of vomiting bile-stained material since birth.

A diagnosis of duodenal obstruction was made on the history, examination and x-ray findings (Fig. 4).

At operation the second part of the duodenum was found to be tightly encircled by an annular pancreas. The enormously dilated proximal and collapsed distal duodenum were dissected out and a duodeno-duodenostomy was performed around the constricting ring of the pancreas. The baby made a satisfactory recovery (Fig. 5).

In two further neonates an annular pancreas was found at necropsy as an incidental finding. In both cases there were no symptoms of duodenal obstruction.

Case 4.—James was admitted on February 26, 1953, aged 3½ weeks, with bronchopneumonia; he died a few hours later.

At necropsy, an annular pancreas,

without duodenal constriction, was discovered (Figs. 6 and 7). Enquiries established the fact that the child had had no symptoms of duodenal obstruction.

Case 5.—David was admitted on March 3, 1953. He had an oesophagotracheal fistula for which an end-to-end anastomosis was performed at the age of 24 hours.

He died of pneumonia one week later, having taken milk feeds and passed milk stools. At necropsy, a ring of pancreas was found surrounding the second part of the duodenum but not constricting it.

Aetiology.—The pancreas of birds is normally annular. The condition has been described in a 16 mm. embryo by Weissberg (1935). The most commonly accepted explanation of this anomaly is persistence of the left half of the central pancreatic anlage.

Signs and Symptoms.—The severity of symptoms and the age at which they occur is presumably determined by the degree of constriction of the duodenum caused by the encircling pancreatic tissue. The adult group comes to surgery for chronic duodenal obstruction, peptic ulceration, or pancreatitis. Presumably some secondary change occurs before the congenital malformation causes symptoms, the degree of obstruction being slight. One might be allowed to speculate that if our two babies, in whom annular pancreas was an incidental finding, had not died, they too might have developed symptoms in later life. The infant group present with complete or incomplete duodenal obstruction at, or soon after birth, and the constriction of the duodenum is severe. Occasionally, obstructive jaundice is present in addition to duodenal obstruction. This has been rather unsatisfactorily explained as being due to pressure on the common duct or ampulla of Vater.

FIG. 6.—Case 4: post-mortem specimen showing the head of the pancreas surrounding the second part of the duodenum.

FIG. 7.—Case 4: horizontal section through the second part of the duodenum. The lumen of the gut is completely surrounded by pancreas. The common bile duct lies medial to the duodenum. The ampulla of one of the pancreatic ducts projects anteriorly into the lumen of the duodenum.

Diagnosis.—In infants, the x-ray films confirm the diagnosis of duodenal obstruction. In none of our three cases had air passed beyond the second part of the duodenum. The films give no clue to the cause of the obstruction and a diagnosis of duodenal atresia is invariably made. Annular pancreas was diagnosed by Lehman (1942) in an adult on the radiographic appearance following a barium swallow. This is the only correct pre-operative diagnosis recorded in the literature. At operation, the diagnosis may be missed in an infant unless the proximal duodenum is dissected free (Case 2). It is perhaps worth noting that none of our 5 infants were mongols, for, in our experience, duodenal atresia is associated with a 50% incidence of mongolism.

Treatment.—In the adult group where obstructive symptoms are less marked, a wedge resection of the encircling ring of pancreatic tissue has been used as an alternative to a short-circuiting procedure. Such a resection would be insufficient in newborn babies as it would not cure the underlying duodenal stenosis or atresia. Duodeno-duodenostomy around the constricting ring of pancreas, if practical, would appear to be the ideal treatment. Failing this,

duodeno-jejunostomy should be satisfactory. Gastro-jejunostomy should be avoided; it will fail to drain the dilated proximal duodenum and incomplete obstruction will result in bile passing backwards into the stomach and the setting up of acute gastritis.*

* Since this paper was prepared we have operated on a further case of annular pancreas in the newborn. This child, however, was a mongol.

I should like to thank Miss I. Forshall for her help with the treatment of these infants and the preparation of this paper.

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PAEDIATRIC SOCIETIES IN THE BRITISH ISLES

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